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# Update on Common Childhood Endocrine Disorders

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## Growth

**G**rowth throughout childhood is an important measure of health and is assessed or documented at each visit from birth. Normal growth can be one of the first signs of either endocrine or non-endocrine disease.

## Overview

Growth is often plotted on growth curves to account for the normal variation in growth velocity over time. Growth in the first year of life is generally very rapid starting at 38 cm/yr in the first few months and dropping to 12 cm/yr by the age of 12 months. Growth velocity continues to decline through early childhood until 5 years of age when it reaches its childhood nadir of an average of 5 cm/yr.<sup>1</sup> The next increase in growth velocity is usually seen in puberty. For girls, this occurs around 9 years of age and for boys is around 11 years. Pubertal growth spurts account for nearly 17% of the final adult height in both girls and boys with growth velocities on average of 9.5 cm/yr in boys and 8.3 cm/yr at peak.<sup>2</sup> This second increase in growth velocity is hormonally dependent, and varies in timing with pubertal development.

Children's genetic height potential can be estimated using parental heights using the following formula (cm):

For males :  $(\text{Mother's height} + 13) + (\text{father's height}) / (2)$

For females :  $(\text{Father's height} - 13) + (\text{mother's height}) / 2$

Typically, a child's final adult height falls within 5 cm of their genetic predicted height. If there is a large discrepancy between the patient's parental heights, this

variation could be larger but a pathological cause should be considered.<sup>1</sup>

## Physical Examination

Physical exam for growth problems must begin with an accurate growth measurement. Children under the age of 24 months should be measured supine using a stationary head board with moveable footplate. This measurement requires two people to accurately perform. One to ensure the patient's head stays firm on the headplate and the second to straighten the knees and move the footplate. When the child is over 24 months of age, standing heights can be obtained. These should not be plotted on the same curve as supine heights. Standing heights are always shorter than supine. Standing heights should be obtained using a measuring device affixed to a wall. Children should stand with their shoes off and heels touching the wall, knees and back straight and chin at a 90° angle to the floor. A 90° object is then placed at the top of the head to mark the height. Measurements should be plotted at the year and month of age on the growth chart. In addition, weight should always be obtained to adequately evaluate growth as well as head circumference for children up to 36 months of age. Additional consideration on physical exam when growth is a concern is that of proportionality. At birth, the upper to lower body segment ratio is 1.7 and then drops to 1.0 by 10 years of age as the limbs grow in length. The physical exam should also include evaluation for any signs of chronic disease such as hepatomegaly, muscular wasting, jaundice, etc. that could contribute to poor growth or stigmata associated with syndromic short stature.

## Diagnostic approach

When determining a child's final adult height potential, it is important to consider their skeletal maturation. Children growing at a higher percentile than expected

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may represent those with some degree of advanced maturation and children growing at a lower percentile may have some delay in skeletal maturation. Skeletal maturation can be determined in children over 3 years of age via an x-ray of the left hand. This x-ray should be read by a clinician with experience in reading pediatric bone age films. Growth plates in the hand are then compared with standards for age.<sup>3</sup> In children younger than 3 years, bone age is determined via the Sontag method which consists of counting the number of growth plates present. This method has higher degree of variability in prediction of true maturation and predicted final adult height. In addition to X-ray evaluation, laboratory evaluation may be obtained. Common evaluation for short stature includes thyroid function testing, celiac screening and growth hormone (GH) screening markers. Growth hormone screening markers, insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGF BP3), are obtained in lieu of GH due to the natural rise and fall of GH levels with peak levels occurring at night. IGF1 levels are a sensitive marker for GH deficiency but IGF BP3 is more specific because this protein is more GH dependent in production.<sup>4</sup> If screening markers are abnormal for GH production, further testing with provocative GH inducing agents and measurement of GH production may be undertaken. Alternatively, overnight GH sampling can be performed. Current testing for adequate GH production is limited by variability in lab assays and poor reproducibility. Therefore, screening and stimulation testing results, should always be evaluated in combination with clinical history.<sup>5</sup> For females with short stature not in concordance with their familial stature, karyotype to rule out Turner syndrome should also be obtained. Additional testing may include bone surveys, genetic testing, or further metabolic workup on a case by case basis.

## Differential for Causes of Short Stature

### Nutritional Short Stature

Cases of non-endocrine short stature often present with decline in growth velocity. Many of these cases

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are also accompanied with poor weight gain that precedes the decline in growth velocity. Workup for failure to thrive obtained due to poor weight gain can often provide clues to the etiology. Chronic diseases associated with poor linear height gain are listed in [Table 1](#).

### Familial Short Stature

Familial short stature is classified by children with an otherwise normal growth velocity whose height, although predicted to be less than 5%, is in line with their parental height prediction. Growth velocity in these children shows a decrease from the age of 6 months until approximately 18 months to 2 years as they decline from their birth percentile to their genetic potential.<sup>6</sup> After the age of 2–3 years they should remain on their percentile. When diagnosing familial short stature, it is important to consider any environmental or genetic factors that may have led to the parental short stature that could be ameliorated in the child.

### Constitutional Delay of Growth

One of the most common variations in growth velocity is constitutional delay of growth. Children with constitutional delay often display normal growth velocity throughout childhood, often following a lower curve than their genetic potential. Around the age of typical puberty growth spurt, these children appear to fall further from their growth curve percentile. This fall is due to the rapid increase in height in standard pubertal children, while those with delay continue at their childhood rate of growth, approximately 5 cm/yr. Physical exam is generally unremarkable in children

**TABLE 1.** Chronic diseases associated with poor linear height gain

Malabsorptive conditions: inflammatory bowel disease, Crohn's disease
Cyanotic heart disease and heart failure
Renal disease
Anemias: sickle cell disease, thalassemia
Diabetes mellitus with poor control (Mauriac syndrome)
Inborn errors of metabolism: glycogen storage diseases, mucopolysaccharidoses, glycoproteinoses, mucopolipidoses
Pulmonary disease
Chronic infection: intestinal and systemic parasites

with constitutional delay aside from a delay in pubertal development. Bone age determination should be obtained in these patients. Children with constitutional delay of growth have a delay in skeletal maturation seen on bone age films. The degree of delay in combination with their current height can then be used to determine their *estimated* final adult height using the Bayley and Pinneau charts.<sup>3</sup>

## ADHD and Stimulant Medications Effect on Growth

At the onset of stimulant medication for ADHD, both weight and height velocity has been shown to significantly decrease in some cases. This attenuated height gain can persist from 6 to 30 months from initiation of treatment.<sup>7</sup> Following this phase, height gain resumes normal velocity. This decline is often accompanied by a delay in pubertal development leading to preservation of final adult height. Peak height velocity and pubertal development have been shown to be delayed significantly in some boys with ADHD treated for > 3 years with stimulants.<sup>8,9</sup>

## Genetic (Syndromal) Short Stature

Short stature is associated with many childhood genetic syndromes. A basic overview of the most common genetic syndromes associated with short stature is listed in Table 2. Some of these children are born small for gestation at birth and other children show decreased growth velocity throughout childhood leading to short stature.

## Thyroid Dysfunction

Hypo/hyperthyroidism is discussed in detail later in this paper but is mentioned here in relationship to growth. Thyroid hormone has been shown to have effect on linear growth through both direct and indirect

measures. Thyroid hormone receptors are expressed on chondrocytes at the epiphyseal growth plate where T3 has been shown to directly regulate chondrocyte expansion and differentiation.<sup>10</sup> In addition, thyroid hormone has been shown to contribute to the control of serum levels of GH and IGF.<sup>11,12</sup> It is through these direct and indirect effects of thyroid hormone that hypothyroidism in childhood and adolescence causes growth arrest, epiphyseal dysgenesis and delayed bone age.<sup>13</sup> With treatment of long standing hypothyroidism, catch-up growth, defined as linear growth velocity greater than expected for age following a period of growth arrest, is seen.<sup>14,15</sup> The magnitude of catch-up growth is limited by the rapid advancement of bone age after treatment of hypothyroidism. Bone age advancement up to twice chronological age advancement has been reported with treatment of prolonged hypothyroidism regardless of pubertal development.<sup>13,14</sup> For this reason, prediction of final adult height on degree of bone age delay prior to treatment leads to an overestimation of actual adult height. Catch-up growth leads to significant improvement in short stature caused by longstanding hypothyroidism in children, but is limited by this rapid bone age advancement leading to final adult heights lower than midparental prediction.<sup>14,15</sup> The degree of deficit in final adult height is related to the duration of hypothyroidism prior to initiation of treatment.<sup>14</sup>

Hyperthyroidism in children also results in deficits in final adult height. Children with untreated hyperthyroidism demonstrate rapid growth accompanied by rapid advancement of the bone age. This ultimately results in early fusion of the epiphyses leading to short stature.<sup>11</sup>

## Rickets

Short stature is a common presenting sign in children with rickets and may be associated with leg deformity.<sup>16</sup> Rickets is caused by hypophosphatemia or hypocalcemia leading to decreased bone mineralization. Hypophosphatemia or hypocalcemia result from a nutritional deficiency of vitamin D or calcium, vitamin D metabolism defects, kidney disease, or hypophosphatemic rickets. Poor bone mineralization seen as a result of these deficiencies is seen at the growth plates in children. As bone weakens around the growth plates, this can result in bony deformity. Toddlers most often present with genu varum (bowing) whereas older children may have genu valgum, kyphosis, or scoliosis

**TABLE 2.** Genetic disorders commonly associated with short stature

Osteochondrodysplasia (achondroplasia and hypochondroplasia)	Noonan syndrome
Down syndrome	Progerias
Turner syndrome	Cockayne syndrome
Russell–Silver syndrome	SHOX deficiency
Seckel syndrome	Prader–Willi syndrome
Albright's osteodystrophy	

as the bones weaken. If the etiology of rickets is nutritional, these deformities and poor growth begin to correct within 3 months of treatment.<sup>17</sup>

### *Glucocorticoid Excess*

Glucocorticoid excess slows growth in children via directly inhibiting longitudinal bone growth. The mechanism of this action is via inhibition of chondrocyte proliferation, hypertrophy, and cartilage matrix synthesis.<sup>18</sup> As a consequence of this growth slowing, there is a delay in growth plate senescence. This allows for a period of catch-up growth similar to that seen in hypothyroidism when excess glucocorticoid exposure is transient.<sup>18</sup>

### *Growth Hormone Deficiency/Insensitivity*

Growth hormone (GH) is produced by the pituitary gland and has long been known to stimulate linear growth in children. Growth hormone action is mediated via induction of protein production in cells. This occurs via binding of GH to two GH receptors leading to dimerization and activation of the JAK/STAT2 pathway. The end result of this activation is increase in IGF-1 production as well as other proteins including IGFBP-3.<sup>19</sup> IGF is the major mediator of growth hormone action through both the serum (from liver production) and locally (via chondrocyte production).<sup>20</sup> Although rare, mutations have been identified throughout the pathway that can lead to GH insensitivity. The most common of these mutations is Laron's dwarfism which involves a mutation of the GH receptor.

In some children, GH production is deficient or insufficient leading to significant reduction in final adult height if not treated with growth hormone replacement. In a study of children with GH deficiency who were untreated throughout childhood, final adult height was found to be as low as  $-2$  to  $-4$  standard deviations (SDS) below the mean.<sup>21</sup> Children with GH deficiency (GHD) may demonstrate poor growth in infancy or may demonstrate deceleration of growth velocity during childhood or pubertal growth. Therefore, GH deficiency should be considered in all children who are demonstrating poor growth velocity.

GH is secreted in a pulsatile nature released during sleep stage 3 and 4 sleep. This makes diagnosis via unprovoked sampling unreliable.<sup>22</sup> Screening for GH deficiency/insufficiency can be done with random sampling, utilizing the proteins IGF-1 and IGF BP3.

As discussed above, these proteins are made in response to GH stimulation and are useful in screening for insufficient GH production due to their longer half-life in the serum and lack of diurnal variation. These screening tests are, however, limited as low IGF-1 levels have decreased specificity early in life when there is significant overlap between GHD and normal individuals. IGF-1 is also altered by nutritional status and is often low when inadequate nutrition is present resulting in false positive results despite normal GH production. In addition, both IGF-1 and IGF BP3 are altered by gender, age, liver function, and pubertal hormones so must always be interpreted against the appropriate normal range.<sup>23</sup> Despite these limitations, when compared with the appropriate normative values, these two tests have combined sensitivity and specificity of approximately 70%.<sup>23</sup> Thus, GH deficiency diagnosis requires more provocative testing even with abnormal screening results.

Provocative testing for GH deficiency is now the diagnostic standard. However, this also has its limitations. The most significant of these limitations include the non-physiologic nature, arbitrary cutoff values for "adequate" growth hormone production, age dependence, questionable role of sex steroid administration, and perhaps the most concerning is the lack of reproducibility.<sup>24</sup> Provocative testing agents include insulin, glucagon, clonidine, arginine, and L-dopa. Generally, two agents are used in combination or sequence to help increase the accuracy of testing. In the United States, positive testing is defined as a peak stimulated GH value of less than  $10 \mu\text{g/L}$ .<sup>5</sup> It has been shown that many prepubertal children will "falsely" fail stimulation testing. However, sex hormone priming prior to GH stimulation testing remains controversial. Some studies report increased specificity of GH stimulation testing after priming, some report no change in GH testing results while other experts believe that priming may lead to under diagnosis of GH deficiency by temporarily augmenting GH secretion.<sup>25</sup> Despite these limitations and controversies, GH stimulation testing remains the accepted "gold standard" for diagnosis of GH deficiency and insufficiency.

## **Treatment for Short Stature**

### *Synthetic Growth Hormone*

Synthetic growth hormone became available for use in 1985 leading to increased indications to aid in



pediatric growth. Its current indications in children as approved by the FDA include treatment of poor growth in Turner's syndrome, SHOX haploinsufficiency, Noonan syndrome, chronic renal failure, and Prader-Willi syndrome. It is also approved for short stature due to growth hormone insufficiency/deficiency, children born small for gestational age without adequate catch up growth, and idiopathic short stature defined as height  $< -2.5$  SD from normal. Synthetic growth hormone has been shown to be most effective when dosed at night via daily subcutaneous injection.<sup>26,27</sup> Dosing is based on weight and the condition being treated as well as individual response. Recombinant growth hormone is a well-tolerated medication with a favorable safety profile. Side effects are rare and include lymphedema, raised intracranial pressure, Carpal tunnel syndrome, slipped capital femoral epiphysis, and gynecomastia. Most side effects resolve with completion of therapy.<sup>28</sup> While concern has been raised about increased risk of cancer with recombinant growth hormone use in childhood, data from pediatric databases and surveillance studies including over 86,000 patients do not support this concern.<sup>28,29</sup> The mechanism of action of synthetic growth hormone is via IGF1 and IGF BP3 production as described above.

### GH Deficiency

The most important predictor of final adult height in GH deficiency is the age of diagnosis and treatment initiation. In the past, GH treatment in GH deficiency has been weight based with a range in dosing from 0.2 to 0.5 mg/kg/wk. On this dose, children usually experience an increase in growth velocity up to 10–12 cm/yr in the first year and then 7–9 cm/yr in subsequent years.<sup>30</sup> There remains some controversy over pubertal dosing of GH to match the typical physiologic rise in GH seen during the pubertal growth spurt. Mauras et al.<sup>31</sup> found a significant increase in height SD from  $-0.7 (\pm 0.9)$  to  $0 (\pm 1.2)$  with no additional adverse events for those who received higher dose GH during puberty. Recently the weight-based dosing approach to GH has been challenged as new studies show that dosing based on IGF1 levels is safer and more cost-effective with similar efficacy as weight based.<sup>32</sup> In addition, mathematical growth prediction models have been suggested as a means to determine GH dosing regimens and reduce variability in response and dosing.<sup>33</sup> However, due to limited access to these mathematical models, this technique

has not become widespread. At this time, the method of dosing and adjustments for growth hormone therapy remains at the discretion of the treating endocrinologist. Additional variables in outcomes of treatment include current height percentile and predicted adult height at therapy start, duration of therapy, and age at start of puberty.<sup>34</sup>

### Idiopathic Short Stature (ISS)

Idiopathic short stature is defined as height below  $-2$  SD without obvious finding of disease. In the United States, GH up to 0.37 mg/kg/wk has been approved for treatment of children less than  $-2.25$  SD.<sup>35</sup> The mean increase in adult height attributable to GH therapy is 3.5–7.5 cm. Responses to GH therapy are highly variable. There are no known serious risks of GH therapy associated with treatment of ISS.<sup>35</sup>

### Small for Gestational Age (SGA) With Failure to Catch up

Small for gestational age is defined as neonates with birth weight or length at least 2 SD below the mean for gestational age. Of these children, some will experience a period of “catch-up growth” but approximately 10% have short stature.<sup>36</sup> If children with SGA remain  $-2$  SD below the mean at the age of 3 years, then they are not likely to catch up spontaneously.<sup>37</sup> In 2001, GH was approved by the FDA for long-term treatment of growth failure in association with SGA at dosages up to 0.48 mg/kg/wk. Growth hormone therapy in SGA is well tolerated with minimal side effects but growth response is variable. This is probably because SGA diagnosis includes a heterogeneous group of children.<sup>38</sup> Higher GH doses appear to lead to more short-term gain in height but long-term height gain appears to be more dependent on cumulative GH dose.<sup>39</sup> A recent study using final adult height measurements rather than predicted heights showed a mean gain in GH treated short stature SGA children to be 1.1 SD with 73% of these children in the normal adult height range. In addition, younger age at start of GH was associated with a better final adult height. In fact, even children started later ( $> 8$  years of age) showed significant increase in final adult height.<sup>40</sup> Currently dosing guidelines on GH therapy for SGA associated short stature are between 0.24 mg/kg/wk and 0.48 mg/kg/wk starting at age 2–3 years and are adjusted based

on the child's response and stature at the discretion of the endocrinologist treating.

## Turner Syndrome

Turner Syndrome is a genetic disorder that affects 1 in 1500–2000 live born females.<sup>41</sup> Girls born with Turner syndrome are born with either one X chromosome (45XO) or are found to have chromosomal mosaicism involving the sex chromosomes with some cells missing an X chromosome or parts of the X chromosome. There are a number of physical abnormalities associated with Turner syndrome with short stature being the most frequent, 80–100% of girls affected display this characteristic. Short stature in Turner syndrome is thought to be due to loss of one SHOX gene, an important gene in bone growth, located in the pseudoautosomal region of the X and Y chromosomes. Growth velocity fails in early infancy and childhood and there is a lack of the typical pubertal growth spurt leading to final adult heights in the  $-2.6$  SD range.<sup>42</sup> Growth hormone at the dose of  $0.3\text{--}0.375$  mg/kg/wk in these individuals improves final height SD by up to  $1.6$  SD.<sup>43</sup> Unfortunately, this final adult height often remains below the normal range. To improve this height gain, there has been some recent interest in the addition of Oxandrolone to GH therapy in Turner Syndrome. Data for this treatment suggests added height gain of on average of  $2.3\text{--}4.6$  cm.<sup>44</sup> As anticipated, there are additional potential side effects and monitoring with combined therapy. More data are needed to make this the standard treatment regimen. Girls with Turner syndrome also have some degree of gonadal dysgenesis leading to incomplete or lack of pubertal development. Manipulation of timing of estrogen replacement and dosing in these girls can also aid in final adult height gain by delaying full maturation of the bones.

## SHOX Haploinsufficiency

Short stature homeobox-containing gene (SHOX) is a gene located on the pseudoautosomal region of the X and Y chromosomes. Therefore, two copies of this gene are expressed in healthy individuals. Mutations of this gene are known to be associated with growth impairment along with variable skeletal anomalies such as madelung deformity. Growth failure in SHOX deficiency starts during the first years of life with puberty height gain relatively unaffected. Untreated mean adult height for SHOX deficiency is on average  $-2.16$  standard deviations below the normal range.<sup>45</sup>

SHOX Haploinsufficiency is an indication for treatment with GH to improve final adult height. Dosing of GH and height gains in SHOX haploinsufficiency are similar to that of Turner syndrome with dosing of  $0.35$  mg/kg/wk.<sup>46</sup> Studies have shown that treatment with GH can result in normalization of or near normalization of final adult height in this population without significant side effects.<sup>46</sup>

## Noonan Syndrome

Noonan Syndrome is a heterogeneous genetic condition with short stature as a feature in the majority of affected patients. Untreated, mean adult height in men is  $63.9$  in and in women is  $60.1$  in.<sup>47</sup> GH is an FDA approved therapy to assist in height gain for those affected. Current dosing of GH in Noonan syndrome is up to  $0.45$  mg/kg/wk. GH therapy has been shown to increase height gain by  $10.9$  cm in males and  $9.2$  cm in females.<sup>48</sup> Earlier initiation and longer treatment leads to improved final adult height outcomes. Another important variable in height gain in Noonan syndrome is age and timing of pubertal development. Untreated, patients with Noonan Syndrome tend to demonstrate further loss in height velocity at normal age of puberty that persists even after their puberty growth spurt. This results in a final adult height loss of approximately  $-0.3$  to  $-0.4$  SD in boys and  $-0.2$  in females if untreated.<sup>48</sup> Overall GH therapy in Noonan syndrome results in significant height improvement in the range of  $+1.4$  SD without any increase in significant side effects.<sup>48</sup>

## Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a genetic syndrome caused by paternal deletion of Chromosome 15 q11–q13 characterized by failure to thrive and hypotonia in infancy followed by obesity and hyperphagia starting around the age of 24 months. Children with PWS have characteristic physical exam findings including short stature along with cognitive and behavioral associations. Growth hormone therapy has been approved by the FDA in the treatment of PWS since 2000 at  $0.24$  mg/kg/wk dosing. It is noteworthy that GH therapy is not solely used for linear height gain in this group but also as a means to increase lean body mass, basal energy consumption, muscle tone, and bone density. In a study by Bakker et al.<sup>49</sup> of 60 PWS patients on GH therapy for 8 years, height SD was noted to increase from  $-2$  SD before treatment to normal height after treatment. Another study comparing height of children with PWS treated with GH vs.

no treatment, showed treated heights of  $171 \pm 8$  cm in boys and  $158 \pm 4$  cm in girls vs. untreated heights of  $154 \pm 9$  cm in boys and  $144 \pm 6$  cm in girls.<sup>50</sup> Height gain in PWS patients who receive GH therapy is well-established with no significant side effects from this medication.

## Aromatase Inhibitors

Without the influence of estrone and estradiol, it has been shown that growth plates remain open and longitudinal growth continues. This has led to the hypothesis that blocking production of these hormones with an aromatase inhibitor in males may lead to increased final adult height. Four randomized controlled trials have now been published that examine the effects of aromatase inhibitors on adult male height. Only one study evaluated final adult height as an outcome rather than predicted height. In a study by Wickman et al., boys with constitutional delay of puberty were given either a combination of testosterone and an aromatase inhibitor (letrozole) or testosterone with placebo. The study reported near final adult height was increased by 1.4 SD in boys treated with letrozole vs. 0.8 SDS in untreated (a mean gain of 6.7 cm in treated over untreated boys).<sup>51</sup> Another study by Mauras has compared anastrozole vs. placebo in combination with GH therapy and found an increase in height of 6.7 cm in those treated for 36 months with anastrozole vs. 1 cm in the placebo group. This study was limited in that heights were predicted and not true final heights.<sup>52</sup> Further studies reported similar results with mean gains in predicted adult height of 0.7 height standard deviations in those treated with letrozole vs. placebo in ISS and 6.1 cm gain in predicted adult height in those treated with letrozole vs. placebo in constitutional delay of puberty.<sup>53,54</sup> Despite these promising data there is concern regarding lack of safety profile information. There has been theoretical concern regarding fertility in males after treatment with aromatase inhibitors as well as bone density concerns, cognitive changes, insulin sensitivity, and lipid abnormalities. Thus far all studies have shown no change in DEXA scan results for bone density, no effect on cognitive function, no increase in HOMA insulin sensitivity index and no influence on sperm parameters later in life in those treated with aromatase inhibitors. Some studies have shown short-term decrease in HDL of unknown clinical relevance. More studies are needed to ensure safety with this therapy.<sup>55</sup> Current

studies are evaluating Letrozole vs. Anastrozole when considering aromatase therapy. Preliminary data suggests benefit of Anastrozole in slowing of epiphyseal maturation leading to increase in predicted adult height with less side effects. Testosterone levels on Anastrozole increase but remain in the upper range of normal in comparison to Letrozole which often produces above normal testosterone levels.<sup>56</sup> Aromatase inhibitors are gaining favor with endocrinologists when predicted final adult height in a male is a concern but there is no indication for starting GH therapy. However, lack of long-term data on safety and efficacy put this therapy in the investigative category.

## Gonadotropin Releasing Hormone (GnRH) Therapy

GnRH therapy has been proposed as a means of increasing height gain around pubertal years by decreasing sex steroid exposure and decreasing bone age progression. Although this initially sounded promising, studies have shown that height gain using this method is minimal at best. GnRH therapy leads to slowing of the growth velocity as well as delayed aging of the bones leading to height gain of only approximately 1 cm per treatment year when used for longer durations (>3 years). Height gain for shorter durations is even more negligible.<sup>57</sup> In addition, there are concerns regarding bone density decrease during therapy with GnRH agonists. GnRH may be used in combination with GH therapy in certain conditions such as late diagnoses of Turner syndrome, GH deficiency, or SGA with short stature. Use of GnRH in these situations is on a case by case basis and is typically in combination with growth hormone therapy.

## Puberty

### Overview and Normal Pubertal Development

Puberty is defined by the appearance of secondary sexual characteristics, transition from sexual immaturity to sexual maturity, and attainment of reproductive capacity. The hypothalamic-pituitary-gonadal (HPG) axis is active in early infancy between 6 and 8 weeks of age, known as the “mini-puberty of infancy”; although no effects on physical development are seen. The HPG axis is then dormant throughout childhood, under a state of active suppression by inhibitory neurotransmitters.<sup>30</sup> Once suppression is released, normal puberty is initiated through pulsatile release of gonadotropin releasing

hormone (GnRH) from the hypothalamus. This results in stimulation of the anterior pituitary gland to secrete gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH); with a relatively greater rise in LH which in turn stimulates sex-steroidogenesis and gametogenesis in the gonads. In girls, LH stimulates estradiol synthesis in the ovaries, while FSH stimulates growth of ovarian follicles. In boys, LH stimulates testosterone synthesis by testicular Leydig cells, while FSH stimulates spermatogenesis in the seminiferous tubules of the Sertoli cells.<sup>1</sup> Activation of the HPG axis, leading to production of sex steroids (gonadarche) occurs concurrently with pubic hair development (adrenarche); these are, however, physiologically distinct events, as adrenarche is not under the control of the HPG axis.

The sequence of pubertal development and progressive physical changes seen in breast, genitals, and pubic hair was first defined by Marshall and Tanner.<sup>58,59</sup> “Tanner staging” consists of systemized descriptions of the development of secondary sexual characteristics; breast changes in females, genital changes in males, and pubic hair changes in both females and males. Tanner staging includes five stages of development, with Tanner stage I representing pre-pubertal status and Tanner stage V representing full adult development. The physical changes seen in Tanner stages are summarized in Table 3.

The first physical sign of pubertal development in girls is thelarche or breast development with onset of breast budding (Tanner stage II). Breast development may initially be unilateral and asymmetrical. Onset of breast budding is followed by growth of pubic hair, linear growth spurt, and lastly menarche. The linear pubertal growth spurt occurs early in puberty, at Tanner stage II breast development. Menarche occurs on average, 2–3 years after the onset of breast development, usually at Tanner stage IV for breast.<sup>58,60</sup>

In boys, the first sign of pubertal development is symmetrical testicular enlargement. Thinning of the scrotum, pubic hair, and linear growth spurt follow. Testicular volume may be measured via a Prader orchidometer<sup>61</sup> or by measuring of testicular length and width.<sup>62</sup> Testicular volume of  $\geq 4$  mL or  $\geq 2.5$  cm in length indicates gonadotropin stimulation and is considered pubertal (Tanner stage II).<sup>63,30,64</sup> Boys reach their linear growth spurt in late puberty at Tanner stage IV, and on average 2 years later than girls. Adult testicular size is considered 18–25 mL.

### Pubertal Timing and Race Considerations

The onset of normal pubertal development has been defined as 8–13 years in girls, and 9–14 years in boy.<sup>58,59</sup> Therefore, any pubertal development prior to

**TABLE 3.** Staging of pubertal development (Tanner)

Staging (girls)	Breast	Pubic Hair	Concomitant changes
I	Pre-pubertal, papilla elevation	No pigmented hair	
II	Budding; larger areole; palpable and visible elevated contour	Pigmented hair, mainly labial	Accelerating growth rate
III	Enlargement of the breast and areola	Coarser, spread of pigmented hair over mons	Peak growth rate, thicker vaginal mucosa, axillary hair
IV	Secondary mound of areola and papilla	Adult in type, but smaller in area; no spread to medial thighs	Menarche (stage III or IV), decelerating growth rate
V	Mature stage, single contour	Adult distribution, spread to medial thighs	

  

Staging (boys)	Genital size	Pubic hair	Concomitant changes	Prader orchidometer (mL)
I	Pre-pubertal	No pigmented hair	Long testis axis (<1.5 cm)	1–3
II	Early testicular, penile and scrotal growth	Minimal pigmented hair at the base of the penis	Early voice changes; testes length 2.5–3.3 cm	3–6
III	Increased penile length and width; scrotal and testes growth	Dark, coarse, curly hair extends midline above penis	Light hair on upper lip, acne, maximal growth, testes length 3.3–4.0 cm	8–12
IV	Increased penis size including breadth; pigmented scrotum	Considerable, but less than adult distribution	Early sideburns; testes 4–4.5 cm	> 12
V	Adult size and shape	Adult distribution, spread to medial thighs or beyond	Beard growth; testes > 4.5 cm	> 15

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the age of 8 in girls, and 9 in boys is considered precocious; while lack of pubertal development after the age of 13 in girls, and 14 in boys is considered delayed.

The average age for onset of breast development in girls is somewhat controversial, although many agree that pubertal onset is trending earlier in US girls and in other developed countries. Furthermore, data consistently suggests that girls enter puberty at varying chronological ages based on their reported race and ethnicity with

African American and Hispanic girls reaching thelarche and menarche at earlier ages compared to Caucasian girls. According to two recent separate studies in the US assessing pubertal development in girls, the average age of pubertal onset for breast development was somewhere between 9.9 and 10.3 years in Caucasian girls and 8.9 and 9.5 years in African-American girls.<sup>65,66</sup> This is in contrast to prior reports in the 1960's which indicated mean age for pubertal onset was much later, closer to 11 years of age for females.<sup>58</sup> On average, menarche occurs at 12.4 years in all races,<sup>67</sup> with slightly earlier menarche occurring in African-American girls (12.1 years) 95% CI [11.87, 12.43] than Caucasian girls (12.6 years) [12.3, 12.9]; Hispanic girls being intermediate (12.31 years) [12.04, 12.59].<sup>68</sup> A recent study examining self-reported age of menarche in US women found that mean age at menarche declined over time from 13.3 years to 12.4 years over the last century with declines observed for all race and ethnic groups.<sup>67</sup>

The average age of onset of puberty in boys detected by testicular enlargement is 11.6 years,<sup>59</sup> although more recent studies have suggested that boys are also entering puberty at an earlier age. Herman-Giddens et al.<sup>69</sup> found that within a population of over 4000 US boys, average age to reach Tanner stage II pubic hair was 10.14, 9.14, and 10.04 years in Caucasian, African-American, and Hispanic boys, respectively; although mean age for reaching testicular volume  $\geq 4$  mL were similar to previously suggested ages and similar between ethnic groups at 11.46, 11.75, and 11.29 years, respectively. Whether or not this actually represents a shift in age of pubertal onset with racial differences is yet to be completely understood.

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***any pubertal development prior to the age of 8 in girls, and 9 in boys is considered precocious; while lack of pubertal development after the age of 13 in girls, and 14 in boys is considered delayed.***

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The reasons for decline in age of pubertal onset and menarche in girls is suggested to be related to improved nutrition and attainment of a critical fat mass/BMI at earlier ages,<sup>70</sup>

alternatively, increased BMI may be associated with later puberty in boys.<sup>71</sup> The effect of environmental factors and role of endocrine disrupting chemicals on pubertal onset is controversial and more studies are needed.<sup>72</sup> Given that age of pubertal onset seems to be occurring earlier than previously noted, some experts have

suggested lowering the age limit for normal puberty to 7 years in Caucasian girls, and 6 years in African American girls<sup>73</sup>; although most pediatricians and Endocrinologist remain most comfortable using the traditional cutoff of 8 years of age in all girls.

## Precocious Puberty

Precocious puberty is defined as secondary sexual characteristics occurring prior to the age of 8 year in girls, 9 years in boys and may be divided into gonadotropin-dependent (central) and gonadotropin-independent (peripheral) causes. A detailed history to determine precise timing of onset of pubertal changes, history of pubertal growth spurt, presence of headaches or CNS symptoms, history of CNS disease or trauma, or history of exposures to exogenous sex-steroids should be elicited. Physical exam should include determination of sexual maturity (Tanner staging) for breast and pubic hair in girls. In boys, measurement of testicular volume should be determined, as well as determination of sexual maturity (Tanner staging) for genitalia and pubic hair. Breast enlargement is indicative of central precocious puberty in girls. An external vaginal exam to evaluate vaginal mucosa should also be performed to assess for estrogenization. Unestrogenized vaginal mucosa will have a glistening red appearance, while estrogenized mucosa will be duller and pink.<sup>1</sup> Estrogenization of the vaginal mucosa is also suggestive of central precocious puberty. In boys, testicular enlargement will be present in a central process; while in peripheral causes of puberty, testes will be pre-pubertal in size ( $\leq 3$  mL). Peripheral visual field testing and fundoscopic exam should be

performed in both girls and boys if there is concern for central precocious puberty. Sex-steroids stimulate linear growth and epiphyseal maturation; therefore children with precocious puberty are tall during childhood but will have premature closure of epiphyses and short final adult height if untreated. A bone age x-ray advanced >2years or +2 SD for age is suggestive of excessive hormonal production/exposure; although a child earlier in their pubertal course may have a bone age less advanced.

## Central Precocious Puberty

Central precocious puberty (CPP) refers to early activation of the hypothalamic–pituitary–gonadal (HPG) axis with secretion of pituitary gonadotropins; and may also be referred to as gonadotropin-dependent precocious puberty. CPP occurs more commonly in girls, and is most often idiopathic in etiology. In boys, CPP is more often pathologic, due to central nervous system (CNS) mass or lesion with hypothalamic hamartoma being the most common. Table 4 lists various causes of CPP.

The diagnosis of CPP should be considered in girls younger than 8 years of age with breast development, or in boys younger than 9 years of age with symmetrical enlargement of the testes, both accompanied by linear growth spurt, or crossing of height isobars on the growth curve. Lab evaluation may reveal pubertal gonadotropins (LH and FSH) and sex-steroids (estradiol in girls or testosterone in boys). An LH:FSH ratio < 1, with FSH predominance is indicative of a pre-pubertal state and suggests inactivation of the HPG axis.<sup>1</sup> A basal LH level of 0.4 U/L or higher is sufficient to make the diagnosis of CPP in girls<sup>74</sup>; while an estradiol level >20 in girls, and testosterone level >50 ng/dL in boys is supportive of the diagnosis.<sup>75</sup> Because gonadotropins are secreted in a pulsatile fashion, daytime/basal levels may initially be low. In those cases where index of suspicion is high, a GnRH stimulation test may be performed by an Endocrinologist for further evaluation of a central

process, or to differentiate a central from peripheral process. If confirmed central precocious puberty, a brain MRI should be obtained to evaluate the hypothalamus and pituitary glands. Treatment is aimed at suppressing gonadotropins and ultimately production of sex steroids by suppressing stimulation of the gonads. In cases with a pathological etiology, the primary problem should be addressed, although it is important to note that most cases of hypothalamic hamartomas do not require surgical intervention. Treatment for idiopathic CPP includes use of long-acting GnRH analog. When children are given GnRH analogs continuously there is paradoxical suppression of gonadotropin release. The most widely used GnRH analog is Lupron Depot, a slow release preparation of leuprolide which is administered by intramuscular injection every 28 days at a typical starting dose of 0.3 mg/kg/dose. More recently, a longer acting 3-months preparation has been demonstrated to give good suppression of puberty.<sup>76</sup> A subcutaneous implant containing histrelin is also available which releases GnRH analog slowly over the course of 12 months.<sup>77</sup> The goals of treatment are to lessen appearance of secondary sexual characteristics, slow linear growth and skeletal maturation, and to inhibit menses in girls. Duration of therapy is determined on a case by case basis with these goals in mind but is typically greater than 2 years. The benefit of treatment on final adult height is greatest if started in early onset CPP (prior to the age of 6 years), and is unlikely to improve final height significantly if started later.<sup>78</sup> Treatment with GnRH analogs have shown to be safe, with no effect on future reproductive function,<sup>78</sup> and progression of normal puberty after cessation of treatment. Menarche typically occurs 12–18 months after stopping treatment although timing is variable.<sup>79,80</sup>

## Peripheral Precocious Puberty

Peripheral precocious puberty (PPP) refers to puberty occurring independent of the HPG axis, due to exogenous exposure or peripheral secretion of hormones from the gonads or adrenal glands; and may also be referred to as gonadotropin-independent precocious puberty. PPP is relatively rare in comparison to CPP. Table 5 lists various causes of PPP.

The hallmark of PPP is secondary sexual characteristics associated with increased linear growth velocity with low or normal levels of gonadotropins (LH and FSH), and no increase in gonadotropins after GnRH stimulation test. Girls and boys with isolated, rapidly

**TABLE 4.** Causes of central precocious puberty

Idiopathic, F > M
CNS tumor: most commonly hypothalamic hamartoma, craniopharyngioma, pinealoma, glioma
Iatrogenic: radiation, chemotherapy, head trauma
CNS infection or abscess
CNS congenital anomalies: septo-optic dysplasia, hydrocephalus, arachnoid or suprasellar cyst
Neurofibromatosis 1

**TABLE 5.** Causes of peripheral precocious puberty

Late-onset congenital adrenal hyperplasia (CAH)
Ovarian or testicular tumor
Virilizing adrenal tumor
McCune–Albright syndrome
Cushing syndrome
Hypothyroidism
Testotoxicosis
Exogenous exposure to sex steroids

progressing virilization, and linear growth acceleration should be evaluated for disorders of androgen excess including late-onset congenital adrenal hyperplasia (CAH), androgen-producing adrenal tumor, androgen-producing ovarian tumor in girls, and testicular Leydig cell tumor in boys. Late-onset CAH is most commonly caused by an enzymatic deficiency of 21-hydroxylase, leading to an increase in its adrenal precursor 17-hydroxyprogesterone (17-OHP). Girls with CAH or androgen-producing tumor may also present with clitoromegaly.

Boys with CAH or androgen-producing tumor will have signs of virilization including penile growth; but without testicular enlargement, helping to differentiate from CPP. Marked asymmetry of enlarged testes or unilateral enlargement with signs of androgen excess and linear growth acceleration suggests testosterone secreting testicular Leydig cell tumor.<sup>1</sup> Cushing syndrome may also rarely present with isolated virilization; although these children usually do not have associated linear growth spurt. Evaluation for virilization includes bone age x-ray and androgens including 17-OHP, DHEA-sulfate (DHEA-S), and testosterone. Measurement of adrenal steroids before and after adrenocorticotrophic hormone (ACTH) stimulation test will identify children with CAH.

In girls, rapidly progressing breast development and linear growth acceleration with significantly elevated estradiol yet suppressed gonadotropins should prompt evaluation for estrogen producing ovarian tumor or McCune–Albright syndrome (MAS). In these girls, pelvic ultrasound may be obtained to evaluate for ovarian cysts or mass. Girls with benign functioning ovarian follicular cysts may present with an isolated episode of vaginal bleeding; these cysts usually resolve without treatment but large cysts may predispose to ovarian torsion. McCune Albright syndrome (MAS) is defined as the triad of PPP, café-au-lait spots, and fibrous dysplasia of the bone. MAS is most commonly seen in girls but may also be seen in boys. Girls often present with recurrent episodes of vaginal bleeding

associated with formation of follicular cysts on pelvic ultrasound. Boys often present with signs of androgen excess such as acne, pubic/axillary hair growth, and penile growth. A thorough skin exam should be performed to look for café-au-lait spots, and plain films will show polyostotic fibrous dysplasia of the bone. MAS is caused by an activating mutation in the gene encoding *GNAS1*, leading to continued stimulation of this protein in endocrine tissues; therefore, other endocrine organs including the thyroid, adrenal, and pituitary gland may also be hyper-functioning.<sup>81</sup>

In boys, testotoxicosis (also referred to as familial male-limited precocious puberty) is a familial cause of precocious puberty, usually presenting by 2–3 years of age with significantly elevated testosterone into the adult range, yet suppressed levels of gonadotropins. There is typically a family history suggesting autosomal dominant inheritance. Boys will present with excessive virilization with enlarged phallus, acne, masturbatory, and aggressive behavior but with disproportionately small testes for the degree of virilization.<sup>82</sup> This is a rare genetic disorder caused by activation of the LH receptor gene and Leydig cell hyperplasia. Ectopic human chorionic gonadotropin (hCG) production from a hCG secreting tumor (germ cell tumor of CNS or hepatoblastoma) may also stimulate abnormally high levels of testosterone production from testicular Leydig cells in boys. Testes may be symmetrically enlarged but also disproportionately small for the degree of virilization. A serum hCG can confirm the diagnosis.

Finally, severe, primary hypothyroidism may cause a pseudoprecocious puberty in both boys and girls with breast development, vaginal bleeding, and cystic ovaries in girls and testicular enlargement in boys.

It is important to note that treatment for gonadotropin-independent precocious puberty or PPP does not respond to GnRH analog therapy as it is not controlled by the hypothalamus. Treatment is directed at the underlying pathology. Children with underlying late-onset CAH are treated from diagnosis with daily glucocorticoid therapy to suppress androgen production. Children with late-onset CAH, although still most commonly caused by 21 hydroxylase deficiency, have a milder mutation and do not have a salt-wasting form. Therefore mineralocorticoid is usually not needed. Tumors of the adrenal, testis, and ovary are treated with surgery, while hCG secreting tumors may be treated with combination of surgery and radiation. Treatment for girls with MAS includes antiestrogens: anastrozole

or letrozole (aromatase inhibitors), and tamoxifen (selective estrogen receptor modulator).<sup>83</sup> Boys with testotoxicosis have been treated with a combination of medications including sprinolactone (androgen receptor blocker) and testolactone (aromatase inhibitor), as well as ketoconazole that inhibits testicular and adrenal androgen production.<sup>83</sup> In children with exogenous exposures to hormones, the removal of the exposure is usually sufficient to promote regression of pubertal changes. The goal of treatment in PPP and CPP is the same: lessen appearance of secondary sexual characteristics, slow linear growth and skeletal maturation, and preserve final adult height.

## Delayed Puberty

Delayed puberty is referred to as the absence of secondary sexual characteristics by age 13 years in girls, and age 14 years in boys.<sup>1</sup> Lack of menarche in girls by age 16 years is also considered delayed (primary amenorrhea). Delayed puberty may be divided into primary and secondary causes. The most common cause of delayed puberty in girls and boys is constitutional delay of growth and puberty, which is discussed under variations of normal pubertal development. It is important to note that causes of delayed puberty here refer to pathology involving gonadarche and the HPG axis, and not pubarche which is under separate control of the adrenal axis.

### *Hypergonadotropic Hypogonadism (Primary Hypogonadism)*

Primary hypogonadism (or hypergonadotropic hypogonadism) refers to failure of the primary end-organ target (ovary or testes) to make sex-steroids. Adolescents with primary hypogonadism have lack of pubertal development with elevated level of gonadotropins by the normal age of puberty (10–11 years) due to lack of feedback to the HPG axis. The most common causes of primary hypogonadism are listed in Table 6.

Turner syndrome is the most common pathologic cause of primary ovarian failure in girls. Girls have associated short stature (discussed previously) and characteristic physical features including broad chest, low hairline, low-set ears, and webbed neck.<sup>84</sup> Right-sided cardiac abnormalities and lymphedema may also be present. Some girls with Turner syndrome may have

**TABLE 6.** Causes of delayed puberty due to hypergonadotropic hypogonadism

Turner syndrome (45, XO) girls
Klinefelter syndrome (46, XXY) boys
Autoimmune ovarian failure
Congenital bilateral anorchia (vanishing testes syndrome)
Chemotherapy, radiation
Infection: mumps, Cocksackie virus, Shigella, malaria, varicella
Trauma or surgical removal

complete lack of pubertal development/estrogen stimulation; while spontaneous initiation of puberty may occur in others.<sup>85</sup> However, girls with Turner syndrome usually experience primary amenorrhea. Pubarche or development of pubic hair is usually normal. A karyotype should be obtained on all girls with short stature and delayed breast development or primary amenorrhea. Fertility is compromised due to few atretic follicles or “streak gonads” and girls with Turner Syndrome require estrogen replacement therapy. Current recommendations are to start low-dose estrogen therapy at 12 years of age, allowing for normalized development of secondary sexual characteristics, as well as uterine and bone mineral development.<sup>85</sup>

Klinefelter syndrome is the most common cause of hypergonadotropic hypogonadism in boys.<sup>86</sup> Clinical features include tall stature, gynecomastia, small firm testes, and low IQ. Boys may have adrenarche and spontaneous initiation of virilization at puberty, but full development of genitalia does not occur. A karyotype showing excess X chromosomes (47 XXY, 48 XXXY, etc.) will reveal the diagnosis.<sup>1</sup> Fertility is compromised due to Sertoli cell failure. Initiation of testosterone treatment is indicated as FSH and LH start to rise to promote secondary sexual characteristics and increase in bone mineral density.<sup>87</sup>

Other causes of primary hypogonadism are discussed here. Autoimmune ovarian failure is an important cause of primary hypogonadism in girls, and may be associated with other autoimmune diseases, including hypothyroidism, adrenal insufficiency, type 1 diabetes, and hypoparathyroidism. Congenital bilateral anorchia (vanishing testes syndrome) refers to testicular regression in boys occurring in utero. The cause of vanishing testes is largely unknown; but thought to be due to perinatal vascular thrombosis or torsion. This probably occurs after 20 weeks of gestation, given that sexual development of external genitalia is normal at birth implying normal testicular function during early pregnancy. Chemotherapeutic drugs, especially the alkylating agents, can be damaging to the ovaries and testes; while local



radiation therapy generally >10–15 Gy may also cause complete primary ovarian failure in girls, while local radiation >6 Gy may cause testicular failure in boys.<sup>88</sup> Infection due to mumps, Coxsackie, Shigella, malaria, and varicella has been associated with oophoritis and orchitis leading to primary hypogonadism in both females and males. Trauma is also an important cause of primary hypogonadism in males.

### Hypogonadotropic Hypogonadism (Secondary Hypogonadism)

Secondary hypogonadism (or hypogonadotropic hypogonadism) refers to failure of the hypothalamic–pituitary axis to secrete GnRH and/or gonadotropins leading to failure of ovarian or testicular stimulation and sex-steroid production. Adolescents with hypogonadotropic hypogonadism have low levels of basal gonadotropins and have no increase in gonadotropins or sex-steroids in response to GnRH stimulation. The most common causes of secondary hypogonadism are listed in Table 7.

Kallman syndrome is a genetic syndrome in both girls and boys in which the hallmark features are hypogonadotropic hypogonadism, infertility, and absent or partially absent sense of smell (anosmia). Kallmann syndrome occurs when the hypothalamic neurons that are responsible for releasing GnRH hormone fail to migrate into the hypothalamus during embryonic development.<sup>30</sup>

Hypopituitarism in girls and boys due to various causes are listed in table 5 and may be associated with signs and symptoms of other pituitary hormone deficiencies including thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and growth hormone deficiencies. Physical exam may show mid-line defects associated with septo-optic dysplasia or absent septum pellucidum. Other causes of central delayed puberty

**TABLE 7.** Causes of delayed puberty due to hypogonadotropic hypogonadism

Kallman syndrome
Hypopituitarism
Head trauma
Congenital structural abnormalities (septo-optic dysplasia, absent septum)
CNS tumor (hypothalamic or pituitary tumor, prolactinoma, craniopharyngioma, germinoma, meningioma, glioma, astrocytoma)
Infiltrative disorders (hemochromatosis, histiocytosis)
Prader–Willi syndrome
Noonan syndrome
Chronic disease
Malnutrition, anorexia

include chronic diseases that involve the heart, gastrointestinal, liver, renal and endocrine systems, as well as malignancy and or chronic infection. Cranial radiation therapy >35–40 Gy in girls and boys may result in GnRH deficiency and secondary hypogonadism.<sup>88</sup>

### Treatment of Hypogonadism

Treatments for permanent causes of primary or secondary hypogonadism are the same; estrogen replacement in girls, and testosterone replacement in boys. In both girls and boys, the initial dose of sex-steroid should be low, and increased gradually over the course of 2 years with the goal of mimicking normal puberty.<sup>89</sup> In girls, estrogen may be given transdermally or orally. Oral conjugated estrogens may be started at 0.3 mg daily; or lower doses, with oral micronized estradiol 0.25 mg/d, or transdermal estradiol 14 µg/d (the lowest available transdermal dose). In women with Turner syndrome, some experts suggest to cut the transdermal patch in half to administer even lower doses of transdermal estrogen (6.25 µg/d).<sup>84</sup> Increases are typically made every 6 months to a year until typical adult doses are reached. Adult doses with transdermal estradiol patch are 100–200 µg daily, 2–4 mg micronized estradiol daily by mouth, or 20 µg ethinyl-estradiol daily by mouth.<sup>84</sup>

For boys, various forms of testosterone supplementation are available but usually long-acting intramuscular injections of testosterone are given every 28 days to initiate puberty.<sup>30</sup> Doses of testosterone enanthate or cypionate are usually started at 50 mg every 28 days and increased every 6 months based on response until adult doses are reached.<sup>1</sup> Testosterone gels and transdermal patches may also be employed, but are not as easily titrated in children. In children with chronic disease, malnutrition or anorexia, treatment of the primary underlying disorder is warranted to enable normal puberty to progress.

## Variations of Normal Pubertal Development

### Premature Adrenarche

Premature adrenarche refers to the presence of pubic hair prior to the age of 8 years in girls, and 9 years in boys and may also be associated with the presence of axillary hair, body odor, and mild acne.<sup>90</sup> Adrenarche occurs independent of the HPG axis and is due to the

physiologic increase in androgens, dehydroepiandrosterone (DHEA) and DHEA-S produced from the adrenal cortex. The phenotype of premature adrenarche varies considerably between populations but may be associated with low birth weight, insulin resistance, adverse cardio-metabolic risk and progression to polycystic ovarian syndrome in some populations.<sup>90</sup> Premature adrenarche is more common in girls than boys and is rare before 6 years of age.<sup>1</sup> Certain ethnicities such as African-American and Hispanic Americans, as well as obese children have higher incidences of premature adrenarche.<sup>68</sup> Premature adrenarche is considered a benign variant of normal in the absence of other signs of puberty. Children with benign premature adrenarche do not have linear growth spurt, signs of androgen excess such as severe acne, clitoromegaly in girls, or phallus enlargement in boys. Evaluation for premature adrenarche should include a bone age x-ray to evaluate skeletal maturity. Skeletal maturity may be minimally advanced but should be within 2 SD of the chronological age.<sup>90</sup> If other signs of androgen excess are present, evaluation may include 17-OHP, DHEA-S, and testosterone, to identify congenital adrenal hyperplasia or an androgen-producing adrenal tumor. DHEA-S is often elevated in children with premature adrenarche, but consistent with Tanner stage for pubic hair. Progression of premature adrenarche may occur, but generally is associated with normal linear growth velocity. Rapid progression or virilization warrants further evaluation.

### *Premature Thelarche*

Premature thelarche is defined as isolated breast development in girls prior to the age of 8 years without other signs of pubertal development. Breast development may be unilateral, or bilateral. The exact cause of thelarche is unknown, but likely due to low, undetectable levels of estrogens and increased sensitivity of glandular breast tissue; although some reports suggest a link with soy products, lavender or tea tree oils.<sup>91</sup> Premature thelarche occurs most commonly in the first 2 years of life, may be present since birth, and generally regresses by 2 years of age.<sup>1</sup> It is important to distinguish premature thelarche from true central precocious puberty; especially given that breast development is the first sign of true puberty in girls. If growth is normal and breast development is minimal, close monitoring of progression is warranted but work up may not be indicated. However, in girls with

Persistence or progression of development or an increase in linear growth velocity, evaluation for precocious puberty is indicated. A small percentage of girls with premature thelarche may go on to development true central precocious puberty.<sup>92</sup>

### *Constitutional Delay of Growth and Puberty*

Constitutional delay of growth and puberty refers to exaggerated delay of puberty (along with linear growth) in otherwise healthy children. Puberty and growth will occur normally, just at a later than average age.<sup>1</sup> There is usually a family history of “late bloomers” in 50–75% of patients with constitutional delay.<sup>93</sup> In these children, pubertal staging and stature are usually commensurate with bone age delay. Predicted final adult height is usually within genetic potential. A diagnosis of constitutional delay of growth and puberty is generally a diagnosis of exclusion, and may be difficult to distinguish from hypogonadotropic hypogonadism. Current literature does not allow recommendation of any diagnostic test for routine clinical use to distinguish these two conditions<sup>94</sup> therefore; these children must be followed closely over an extended time period until puberty begins or until their late teenage years. Some endocrinologists advocate for a course of short-term hormonal treatment in children who are expressing substantial anxiety over their delay as initiation of treatment has been shown to induce puberty in cases of congenital or functional hypogonadotropic hypogonadism, including constitutional delay<sup>95</sup>; but generally not prior to age 14 years of age.<sup>94</sup>

### *Gynecomastia*

In pubertal boys, breast enlargement, termed gynecomastia is almost always due to benign physiologic pubertal gynecomastia. Pubertal gynecomastia may occur in 50–60% of normal pubertal boys<sup>96</sup> and usually self-resolves by completion of puberty. Pubertal gynecomastia occurs due to relative imbalance between estrogen and androgen serum concentrations. The diagnosis of gynecomastia is made on physical examination as palpable glandular or rubbery tissue, 0.5 cm or larger, underlying the nipple which may be tender, unilateral or bilateral, and often asymmetric. True gynecomastia should be distinguished from pseudogynecomastia, which is due to an increase in fatty tissue. Pathological causes of gynecomastia in adolescent boys are uncommon but include hypogonadism, recreational drug use, chronic liver or kidney disease,

and human chorionic gonadotropin secreting tumor. Since pubertal gynecomastia will resolve in almost all boys, no treatment is usually warranted. Treatment with anti-estrogens anastrozole<sup>97</sup> has been shown to be ineffective; although tamoxifen has some benefit.<sup>98</sup>

## Thyroid

The thyroid gland secretes thyroxine (L-tetraiodothyronine) or T4 and triiodothyronine or T3. Thyroid hormone action is accomplished by T3, converted from T4 which is considered to be a prohormone. Another type of cell is present in the thyroid gland known as parafollicular or C cells; these cells produce the polypeptide hormone calcitonin. Thyroid hormones have many important biological effects including control of basal metabolic rate, stimulation of neural development and normal growth, and support for cardiac function. Thyroid hormone synthesis is regulated by the pituitary via thyroid stimulating hormone (TSH).<sup>99</sup>

For the assessment of thyroid function, generally, determination of the serum concentrations of free T4 and TSH are sufficient. It is essential that age-specific reference ranges are applied and that the interpretation is based on a thorough knowledge of thyroid physiology. Also, there are discrepancies between different laboratory methods, therefore it is necessary that each laboratory provide method-specific reference ranges. These factors should accordingly guide interpretation of the serum hormone levels.<sup>100</sup>

## Euthyroid States

There are certain conditions in newborn, childhood, and adolescence characterized by generally euthyroid states. These include the following: obesity-related TSH elevation, nontoxic or simple goiter, thyroxine-binding globulin deficiency, and hypothyroxinemia in the newborn. These conditions either do not merit therapy or the beneficial effect of thyroxine therapy is controversial. These conditions are discussed further below.

### *Elevated TSH Levels in Obesity*

Studies on the thyroid function in overweight and obese children have shown slightly higher TSH values with normal T4 but elevated T3 levels.<sup>101,102</sup> There are still a lot of unanswered questions regarding the mechanism behind these findings. The most favored

hypothesis is the increase in leptin-mediated production of TRH in the hypothalamus related to elevated BMI which eventually leads to increased TSH. Leptin is a hormone released from the adipocytes that circulates at levels proportional to the body's adiposity.<sup>103,104</sup> The elevated free and total T3 levels is due to increased activity of extrathyroidal monodeiodinase; this is thought to be an adaptive response designed to increase energy expenditure. Abnormalities in thyroid function and TSH mostly normalize after weight loss independently of whether the loss is the result of diet or bariatric surgery. Therefore, in the majority of cases of slightly higher TSH in obesity, no thyroid supplementation is needed, since TSH level normalizes once weight loss is attained.<sup>102,105</sup>

### *Simple Nontoxic Goiter*

Goiter or thyromegaly are synonymous terms which are used to describe an enlargement of the thyroid gland. It is reported to occur in 1–3% of normal adolescent population in the US between the age of 11 and 18 years with female to male predominance. Simple nontoxic goiter is frequently noted at puberty and the cause is usually ambiguous. But possible causes include intrinsic thyroid hormone production defects, iodine deficiency, or intake of drugs that can decrease synthesis of thyroid hormone. The hypertrophy may be diffuse or nodular and is not associated with hypothyroidism, hyperthyroidism, or inflammation. Except in severe iodine deficiency, thyroid function is normal and patients are asymptomatic except for an enlarged, nontender thyroid. Diagnosis is clinical and levels of free T4 and TSH are normal.<sup>106</sup>

### *Thyroxine-Binding Globulin Deficiency*

Thyroxine-binding globulin (TBG) is the major serum binding protein for thyroxine and triiodothyronine. TBG deficiency does not alter metabolic status but it leads to decreased serum level of total T4, which may be misinterpreted and may result in an inappropriate diagnosis of hypothyroidism. TBG deficiency presents with low serum T4 level, normal serum free T4, normal TSH level, and low serum level of thyroid hormone binding globulin.<sup>107</sup> Inherited TBG deficiency may present as either a complete or partial deficiency. The incidence of complete TBG deficiency is 1 in 15,000 while partial TBG deficiency occurs in 1 in 5000. This is an X-linked condition. The low serum total T4 and normal TSH may

be detected in newborn screening. Since serum free T4 and TSH are within normal range, these infants are euthyroid; and do not require treatment.<sup>108</sup>

### *Hypothyroxinemia of Newborn*

Transient hypothyroxinemia is characterized by low serum free/total T4 levels without elevation of serum TSH. It is the most common thyroid dysfunction in preterm infants. It is present in majority of infants born at less than 30 weeks gestation. The etiology of transient hypothyroxinemia is not clear but various hypotheses have been considered such as hypothalamic–pituitary–thyroid axis immaturity, withdrawal of maternal–placental T4 transfer, iodine deficiency, and nonthyroidal illness.<sup>109</sup> It is not known if there is a linear correlation between the degree of lowering of T4 and negative outcomes, such as short-term mortality and long-term morbidity (developmental problems). Randomized placebo controlled studies of thyroxine supplementation in premies have not found an overall benefit in terms of morbidity, mortality, or developmental outcome. In fact, although the mechanism was not clear, lower IQ's were observed in thyroxine-treated infants born after 27 weeks of gestation.<sup>1</sup> Hypothyroxinemia of prematurity generally resolves by 6–10 weeks of age. However, some preterm infants go on to have delayed TSH elevations. For these reasons, serial TSH and Free T4 screening is recommended for premature infants at 2, 6, and 10 weeks of age.<sup>110</sup>

Acutely ill neonates also tend to have lower total and free T4 values. Because of the crucial role of thyroid hormone in the developing nervous system, experts have advocated empiric thyroid hormone treatment in acute illness. T4 treatment has decreased critical care and inotrope needs, but benefit to neurodevelopmental outcome has not been established. Recovery from the acute severe illness is generally followed by normalization of free T4 and TSH levels. However, if TSH elevation persists after recovery from the illness, treatment with thyroxine is started to protect cognitive function. In these treated cases, thyroxine may be provided until the third birthday when rapid brain growth is complete. At age 3 years, trial off of thyroxine followed by sequential thyroid function testing can determine if there is permanent thyroid dysfunction.<sup>111</sup>

## **Congenital Hypothyroidism**

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation.

Most children with CH require lifelong hormone therapy due to abnormality in their thyroid gland's development or thyroid hormone production. However, sometimes abnormal thyroid function is transient, and treatment may be temporary or not necessary.<sup>112</sup> In areas where iodine deficiency is high, infants and children are at risk for endemic cretinism, while in iodine-sufficient areas, the occurrence of congenital hypothyroidism is sporadic.<sup>111</sup>

### *Permanent Congenital Hypothyroidism (CH)*

The most common cause of permanent CH is thyroid dysgenesis. This affects 1 in 4000 newborns and comprises about 80–85% of permanent CH. This is due to developmental defects of the thyroid gland. Defects may include arrested migration of the embryonic thyroid in the sublingual area (ectopic thyroid), complete absence of thyroid gland (athyreosis), or partial absence of thyroid tissue (hypoplastic thyroid).<sup>108,113</sup> Thyroid dysgenesis is usually sporadic and has a female to male ratio of approximately 2:1. Certain ethnic groups such as Hispanic, Asian, and Native American are at increased risk for developmental thyroid anomalies. African-Americans are at reduced risk with 1/3 the risk compared to European descent Americans.<sup>111</sup> Only 2% of infants with thyroid dysgenesis have a familial disorder due to mutations in the genes that control thyroid differentiation such as TTF-1/NKX-2, TTF-2/FOXE-1, and PAX-8 genes. Nonthyroidal congenital anomalies and conditions (heart defects, respiratory distress, cleft lip and palate, and spiky hair) are also found in infants with thyroid genetic defects.<sup>114–116</sup>

Another cause of permanent CH is thyroid dysmorphogenesis. These children comprise 10–20% of permanent CH cases, occur in 1 in 40,000 births, and display autosomal recessive inheritance. Thyroid dysmorphogenesis disorders involve functional defects in one of the steps involved in thyroid hormone biosynthesis such as abnormalities in responsiveness to TSH, iodide trapping, organification defects, thyroglobulin synthesis, and iodothyronine deiodination. An abnormal chloride–iodide transport protein may also present with congenital sensorineural hearing loss in the condition referred to as Pendred syndrome. Most affected infants with thyroid dysmorphogenesis develop goiter that may or may not be present at birth.

Congenital central hypothyroidism is a more rare etiology of permanent CH. It has an incidence of



1:50,000 to 100,000 newborns being affected. It is caused by insufficient TSH stimulation of a normally located thyroid gland. Most patients have low free thyroxine levels and inappropriately low or normal TSH levels.<sup>117</sup> In this condition, there are anomalies of the brain that cause abnormal hypothalamic and/or pituitary function. These children may also present with deficiencies of growth hormone, ACTH, TSH, and gonadotropins. Possible etiologies include absence of the septum pellucidum and other midline defects as well as pituitary stalk interruption, pituitary ectopia, empty sella syndrome, and pituitary hypoplasia/aplasia. Congenital hypopituitarism may also result from mutations in transcription factor genes (PROP-1, Pit-1, HESX1, and LHX4) involved in pituitary gland development or function. Isolated familial TSH deficiency is usually due to mutations in the TSH *B*-subunit or in the TRH receptor gene.<sup>108,117,118</sup> See Table 8 for an overview and classifications of congenital hypothyroidism.

### Transient Congenital Hypothyroidism

Approximately 5–10% of infants with positive screening identified by the newborn screening programs have transient hypothyroidism. This is characterized by low or normal free T4 and variable elevations of serum TSH. Causes transient congenital hypothyroidism are: (1) transplacental passage of either antithyroid medication used to treat maternal Graves' disease, or TSH receptor-blocking autoantibodies from a mother with autoimmune thyroid

disorder. (2) Infants born in areas with endemic iodine deficiency and those exposed to excess iodine. Clinical course varies in duration from 1 week to approximately 4 months. Thyroid hormone replacement is indicated if low free T4 levels and/or elevated TSH persist over a few days. Thereafter, the dose can be safely weaned and finally discontinued once thyroid function normalizes around 4 months of age.<sup>108</sup>

## Diagnosis of CH

The diagnosis of primary hypothyroidism is made based on the presence of elevated serum TSH and low or normal free T4. The diagnosis of secondary hypothyroidism is made when free T4 is low and TSH is low or normal. Newborn screening (NBS) has been an invaluable tool in the diagnosis of CH because most affected infants do not have obvious clinical manifestations of hypothyroidism at birth. It has facilitated early diagnosis and treatment of these affected infants within 1–2 weeks of age, normalizing their neurodevelopmental outcome.<sup>111</sup>

### Newborn Screening

In the 1970s, the ability to detect T4 and TSH in dried blood specimens utilizing radioimmunoassay methodology was developed, and subsequently incorporated into public health newborn screening programs. Before the onset of newborn screening (NBS), the incidence of CH based on clinical diagnosis was approximately 1:7000. With NBS since mid-1970s, the identification of cases increased to 1:4000. A more recent analysis reported that the incidence in the US increased from 1:4094 in 1987 to 1:2373 in 2002.<sup>119</sup> One reason attributed to the higher incidence in abnormal NBS is earlier discharge from the hospital leading to NBS specimens being obtained during the physiologic TSH surge which occurs within 72 h of life. Other reasons are lowering of TSH cutoff and increased incidence of prematurity.<sup>119</sup>

At birth and exposure to the cold extrauterine environment, TSH (and consequently, T4) surge occurs within minutes of birth and subsides over the next 24–72 h. This physiologic surge also occurs, but in a stunted fashion, in preterm infants. Thus, the ideal collection time for CH screening is at 3–5 days of age to optimize both sensitivity and specificity of screening. Most screening programs require a follow-up

**TABLE 8.** Classification of congenital hypothyroidism<sup>100,111</sup>

Permanent congenital hypothyroidism
Primary hypothyroidism
Thyroid dysgenesis
Ectopic thyroid gland
Hypoplastic thyroid gland
Athyreosis or Aplastic thyroid gland
Thyroid dysmorphogenesis
TSH binding or signaling resistance
Iodide-trapping defect
Organification defect
Thyroglobulin defect
Iodotyrosine deiodinase deficiency
Secondary or central hypothyroidism
Malformation of hypothalamus, pituitary gland
Genetic defects (PROP-1, Pit-1 mutations, HESX1, LHX3 gene mutations)
Isolated TSH deficiency
Generalized thyroid hormone resistance
Transient congenital hypothyroidism
Maternal intake of antithyroid medication during pregnancy
Maternal thyroid stimulating/receptor blocking antibody
Deficiency or excess iodide
Idiopathic

specimen if the initial specimen is collected at <24 h to minimize the chance of missed diagnosis.<sup>111</sup>

Currently, there is mandatory universal newborn thyroid screening in the US, Canada, Europe, Australia, in some parts of Asia, the Middle East, and Latin America. There are three types of thyroid newborn screen strategies: (1) primary T4, secondary TSH: where all newborns are screened for total T4 and with TSH measured in those with T4 below a cut-off value and for a certain percentile of the screened population. This approach enables detection of central and peripheral hypothyroidism, as well as TBG deficiency and hypothyroxinemia in premature infants.<sup>120</sup> (2) Primary TSH, with or without secondary T4: this strategy provides a mechanism for monitoring for regions of iodine deficiency because it provides information about mean TSH for specific populations. It also detects those patients with subclinical or compensated hypothyroidism where T4 is maintained in the normal range with elevated TSH.<sup>120</sup> (3) Combined initial T4 and TSH: may be the most sensitive and specific approach currently in use. This strategy detects secondary or central hypothyroidism as well as subclinical hypothyroidism.<sup>120</sup> The strategy utilized the newborn screen for hypothyroidism detection varies by state in the U.S.

Indications for follow-up screening test are: very low birthweight infants <1500 g, any birthweight baby with perinatal complications, NICU admission, transfusion, congenital heart disease, other severe congenital anomalies, same sex twins and drug exposure to steroids, dopamine and iodine.<sup>120</sup>

### *Diagnostic Studies to Determine Underlying Etiology of CH*

Once an infant is confirmed to have primary CH, additional diagnostic studies may be undertaken to determine a specific etiology. Because results from these additional diagnostic tests do not alter the initial treatment decision, they may be considered optional. Starting thyroid hormone treatment should never be delayed by more than a few days (to perform these additional studies).

These additional studies include thyroid radionuclide uptake and/or scan and thyroid ultrasound.<sup>123</sup> Iodine or sodium pertechnetate 99m (Tc<sup>99m</sup>) will identify thyroid aplasia, hypoplasia (decreased uptake, small gland in eutopic location), an ectopic gland (thyroid tissue located at the base of the tongue), and a gland in the normal location over the thyroid cartilage. Absent

radioiodine uptake, typically diagnostic of thyroid aplasia, can also be seen in the presence of maternal TSH receptor-blocking antibodies (TRB-Ab), iodide-trapping defects, TSH receptor-inactivating mutations, and TSH beta gene mutations. To differentiate these conditions from true absence of the gland, thyroid ultrasound is useful. Infants with these apparent athyreosis will show presence of the thyroid gland on ultrasound. Of course, infants with true athyreosis will have no thyroid gland visualized on ultrasound. Measurement of TRB-Ab and specific genetic testing in infants with athyreosis will help determine whether TRB-Ab or genetic cause is present. In cases of thyroid dysmorphogenesis, the thyroid ultrasound will show an enlarged thyroid gland in the normal location.<sup>118</sup> See Table 9 for signs and symptoms of hypothyroidism in neonates and infants.

## **Treatment of Congenital Hypothyroidism**

### *Initial Therapy*

The decision to treat should be made as soon as the diagnosis is either proven or extremely likely. It is very important for patients with severe hypothyroidism to be treated no later than the first 2 weeks of life. Levothyroxine is the treatment of choice for CH. The recommended starting dose is 10–15 µg/kg/d, to be given orally

**TABLE 9.** Signs and symptoms of hypothyroidism in neonates and infants<sup>103,114</sup>

Neonates
Postmaturity (gestational age > 42 wk)
Hypothermia
Prolonged jaundice
Hypotonia, inactivity
Poor feeding, abdominal distention
Macrosomia (BW > 4 kg), edema of eyelids, hands, and feet
Open posterior fontanelle (> 5 mm) and/or large anterior fontanelle
Generalized delay in skeletal maturation (but normal birth length)
Infants and older
Decreased muscle tone, lethargy
Poor suck or feeding and failure to gain weight
Hypothermia
Decreased stool frequency/hard stools
Respiratory distress, hoarse cry
Macroglossia, coarse facial features
Abdominal distention, umbilical hernia
Dry and mottled skin
Generalized swelling or myxedema
Deceleration of linear growth, skeletal retardation, delayed eruption of teeth and in shedding of primary teeth
Muscle weakness, muscular pseudohypertrophy

at one dose per day. Its long half-life makes daily dosing practical and there are no consequences of an occasional missed dose. L-thyroxine is converted to the active hormone T3. In the brain, local T4 to T3 conversion is especially important. This observation supports the rationale for treatment with L-thyroxine in pediatric patients. In addition, all of the large scale outcome studies for treated cases of CH have utilized L-thyroxine. Thus, treatment of congenital hypothyroidism with T3 is not recommended in this age group.<sup>111,121</sup>

L-thyroxine is available as a scored tablet of synthetic hormone in a variety of doses. In infants brand medication is often used for consistency of dosing. Generic may be utilized if the generic supplier remains constant. The tablets should be crushed and suspended in 5–10 mL of water and given immediately by a spoon or dropper. The crushed tablet may also be sprinkled over a small amount of food (applesauce or cooked cereal). Foods containing large amounts of soybean, fiber, or iron should not be used for administering the medication. Even though the administration of L-thyroxine on an empty stomach may be better than absorption with or after meals, the more important aspect in the administration is consistency combined with regular monitoring of serum hormone levels followed by appropriate dose adjustment.<sup>122</sup>

Monitoring therapy is accomplished by determination of serum free T4 and TSH. It is recommended to measure serum hormone levels 2 weeks after the start of L-thyroxine therapy. The aim is rapid normalization of free T4 in the upper half of normal range within 1–2 weeks of starting treatment. TSH levels generally decrease to normal range within a month of starting L-thyroxine treatment. Thereafter, TSH should be maintained in the normal range. Serum free T4 and TSH should be monitored every 1–2 months for the first year of life, then every 2–3 months until age 3 years, and every 3–6 months through childhood and adolescence until growth is complete. When dose adjustments are made, follow-up testing should be performed in 2–4 weeks. A rise in TSH while on treatment generally confirms the need for an increase in dosing and ongoing replacement therapy (provided there has been good treatment compliance).<sup>118,121</sup>

Resistance (poor absorption, enhanced clearance, and pituitary/peripheral resistance), and noncompliance may present with persistent TSH elevation despite thyroxine therapy. On the other hand, adverse effects

due to prolonged hyperthyroxinemia are craniosynostosis and osteoporosis. These effects can be avoided by regular monitoring of thyroid function tests and avoidance of overtreatment.<sup>111</sup>

## Acquired Hypothyroidism

### *Autoimmune Thyroiditis*

Autoimmune thyroid disease or Hashimoto's thyroiditis is the most common etiology of acquired thyroid dysfunction in children and adolescents. It is also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis. In one retrospective study of 153 patients <18 years with Hashimoto's thyroiditis: 47.1% were euthyroid, 31.4% had subclinical hypothyroidism, 14.4% presented with overt hypothyroidism, and 7.2% were hyperthyroid. Prevalence in childhood of autoimmune thyroiditis peaks in early to mid-puberty and has a female preponderance of 2:1.<sup>123</sup>

This condition is associated with antibodies against thyroid peroxidase and thyroglobulin and in hyperthyroid individuals, TSH receptor antibody is present as well. It is characterized by lymphocytic infiltration of the thyroid gland, which results in thyromegaly. Damage to the thyroid gland reflects both antibody-mediated and cell-mediated injury.<sup>124</sup>

There are 3 types of autoimmune thyroiditis characterized by the presence of thyroid autoantibodies:

- (1) Type 1 autoimmune thyroiditis (Hashimoto's disease): euthyroid individuals as evidenced by normal serum TSH.
  - a. Type 1A: goitrous.
  - b. Type 1B: nongoitrous.
- (2) Type 2 autoimmune thyroiditis (Hashimoto's disease):
  - a. Type 2A: goitrous or classic Hashimoto's disease with increased TSH.
  - b. Type 2B: nongoitrous -atrophic thyroiditis with increased TSH.
  - c. Type 2C: transient aggravation of thyroiditis (e.g., postpartum thyroiditis); may start with transient thyrotoxicosis and followed by hypothyroidism.
- (3) Type 3 autoimmune thyroiditis (Graves' disease): stimulatory autoantibodies to the TSH receptor are present as well as anti-TPO and Anti-TG antibodies.

- a. Type 3A: hyperthyroid Graves' disease.
- b. Type 3B: euthyroid Graves' disease.  
Type A and B have suppressed TSH.
- b. Type 3C: hypothyroid Graves' disease: presence of exophthalmos with hypothyroidism.

### Clinical Presentation of Autoimmune Hypothyroidism

The presentation of chronic autoimmune thyroiditis includes either hypothyroidism, goiter, or both. A goiter or firm thyroid is the first physical sign of chronic autoimmune thyroiditis. Thyromegaly is typically diffuse with a "pebbly" or "seedy" surface that evolves into a firm and nodular consistency.<sup>124</sup> Initial history may reveal disturbances in energy level, sleep pattern, menses, cold intolerance, and school performance. In addition to visualization and palpation of the thyroid, assessment of extraocular movements, edema, and deep tendon reflexes are important components of physical examination. Growth and pubertal development need to be assessed since growth failure may be present. Pubertal delay may occur but, as discussed previously, pseudoprecocious puberty manifested by testicular enlargement in boys younger than 9 years old and breast development in girls younger than 8 years old has been reported.<sup>124</sup>

Chronic autoimmune thyroiditis may be the initial presentation of autoimmune polyglandular syndrome, and the possibility of coexisting autoimmune diseases such as type 1 diabetes, Addison's disease, and pernicious anemia should be addressed by the past medical history and review of systems. See Table 10 for symptoms/signs of acquired hypothyroidism.<sup>124,125</sup>

### Diagnosis of Acquired Hypothyroidism

Serum TSH is elevated in primary hypothyroidism, thus it is an appropriate screen for acquired hypothyroidism. However, both serum TSH and free T4 are typically obtained in the initial blood work to screen for hypothyroidism. In mild hypothyroidism, serum T3 can remain in the normal range due to the increased conversion of T4 to T3 and the preferential secretion of T3 by residual thyroid tissue under the influence of the high TSH level. For these reasons, measurement of serum T3 is not a useful test in the diagnosis or monitoring of patients with primary hypothyroidism.

**TABLE 10.** Symptoms and signs of acquired hypothyroidism adapted<sup>114,117</sup>

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Goiter or thyromegaly
Linear growth deceleration with or without short stature
Delayed eruption of teeth and shedding of primary teeth
Skeletal maturation delay
Pubertal disorders (delay or pseudoprecocity)
Lethargy and impaired school performance
Easy fatigability
Infrequent and hard stools
Cold intolerance
Hypothermia
Dry, scaly skin
Bradycardia (decreased cardiac output)
Delayed deep tendon reflexes
Muscle weakness
Generalized swelling and myxedema
Fluid retention and weight gain (impaired renal free water clearance)

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The presence of goiter or elevated TSH should prompt the measurement of anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin). Anti-TPO is the more sensitive screen for chronic autoimmune thyroiditis compared to anti-TG.<sup>111</sup> Typically, obtaining anti-TPO as well as anti-TG will help establish the autoimmune etiology for hypothyroidism or goiter. Up to 90% of patients with hypothyroidism secondary to autoimmune thyroiditis are anti-TPO antibody positive. It should be noted that 10–15% of the general population are positive for anti-TPO antibodies.<sup>111</sup> If anti-TPO antibodies are absent, less common etiologies of primary hypothyroidism such as transient hypothyroidism (post-subacute thyroiditis), external irradiation, and consumptive hypothyroidism should be considered.

Subclinical hypothyroidism is defined as TSH elevation with normal concentrations of circulating free T4. The log-linear relationship between serum TSH and free T4 explains how small reductions in serum free T4 lead to large increase in TSH. The majority of these patients are asymptomatic, but studies in the adult population suggest that individuals with the combined risk factors of elevated TSH and positive thyroid antibodies are at high risk for progression to overt hypothyroidism.<sup>111</sup>

### Treatment of Acquired Hypothyroidism

Levothyroxine (L-T4) is the replacement of choice in children with hypothyroidism. Its long half-life of 5–7 days allows the convenience of daily administration and a gradual equilibration over the course of 5–6 weeks. The dose of replacement thyroxine decreases on a weight basis with age, although it approximates



100 µg/m<sup>2</sup>/d. Dosing should ultimately be individualized on the basis of biochemical monitoring. Table 11 shows the recommended starting treatment doses (µg/kg body weight) by age.

TSH normalization is the goal of replacement; free T4 should be in the upper half of normal range. Thyroid function tests should be obtained 4–6 weeks after the initiation or adjustment of the L-T4 dose. Growth and sexual development should be followed. Once biochemical euthyroidism has been achieved, TSH can be monitored every 4–6 months in the growing child and annually once final height has been attained. Overtreatment as evidenced by abnormally high freeT4 and suppression of TSH below the normal range, should be avoided since this may advance skeletal maturation too rapidly and compromise final adult height.<sup>111,124</sup>

Adverse reactions to L-thyroxine are rare. Pseudotumor cerebri had been reported after initiation of L-thyroxine, thus some have advocated a slower more gradual increase in dosing for the medication. A variety of drugs may alter L-thyroxine requirements. In theory, L-thyroxine should be administered at least 30 min before eating or taking any medication known to impair its absorption (i.e., soy, iron, and calcium). However, from a practical viewpoint, the most important goal is to establish a regular time for L-thyroxine administration. Monitoring of thyroid function is lifelong. Parents of children with chronic autoimmune thyroiditis should be advised that the hypothyroidism will likely be permanent.<sup>126</sup>

## Drugs/Medications That Affect Thyroid Function

A large number of drugs or medications may affect thyroid function. There are several mechanisms through which this may occur. Ultimately there may be a need to maintain patients using these drugs on

L-thyroxine if they become hypothyroid. Thus periodic monitoring of thyroid function is a recommended for patients taking these medications.

1. Drugs affecting thyroidal synthesis of T4 or T3:
  - a. *Lithium carbonate*: long-term treatment with lithium may lead to goiter in approximately 50% of patients taking the drug and may induce subclinical (34%) or overt (15%) hypothyroidism.<sup>123</sup> It inhibits thyroid hormone synthesis and release, has a cytotoxic effect, and can lead to increased thyroid autoimmunity. Factors that increase risk for lithium toxicity are presence of thyroid antibodies, female gender (5:1), older age, and > 2 years of therapy.<sup>123</sup> Therefore, thyroid function and presence of autoantibodies should be evaluated at the start of therapy and every 6 months while on lithium therapy. L-T4 therapy is started once hypothyroidism develops, lithium treatment may be continued.
  - b. *Amiodarone and other iodinated drugs*: these drugs present excess amounts of iodine to the body, thus can induce hypothyroidism in about 5–15% of patients with the highest risk during the first 18 months of treatment.<sup>123</sup> Individuals at risk for hypothyroidism are patients with positive thyroid antibodies, women, elderly and those living in iodine-sufficient areas.
  - c. *Cytokines*: alpha and beta interferon, interleukins, and granulocyte macrophage colony-stimulating factor have been associated with hypothyroidism and the development of thyroid autoimmunity. Risk factors for the development of hypothyroidism in patients treated with cytokines include female gender, prolonged duration of treatment, advanced age, and preexistent thyroid autoimmunity. Pre-treatment screening is recommended for all patients to be treated with cytokines. The development of thyroid autoantibodies and the onset of hypothyroidism are not contraindications for starting therapy with cytokines, but L-T4 therapy should be started as soon as hypothyroidism is documented.
  - d. *Tyrosine kinase inhibitors (TKIs)*: are antineoplastic agents and hypothyroidism can result possibly from following mechanisms: inhibition of thyroid iodine uptake, inhibition of thyroid peroxidase, toxic effect with the development of

**TABLE 11.** Dose of levothyroxine (micrograms [µg]/kilogram [kg]) of body weight for age

Age	µg Levothyroxine/kg body weight
0–3 months	10–15
3–6 months	8–10
6–12 months	6–8
1–3 years	4–6
3–10 years	3–4
10–15 years	2–4
15 years	2–3

painless destructive thyroiditis, or increased in D3 deiodinase activity.

- e. *Other drugs/substances*: resorcinol may inhibit TPO and cause reduced thyroid synthesis. Thalidomide decreases thyroid hormone via an unknown mechanism. Soy protein supplements may increase the need for L-T4 by reducing GI absorption.<sup>123</sup>

## 2. *Drugs interfering with thyroid hormone (TH) transport*

- a. *Estrogen, androgens*: estrogen increases thyroid binding globulin (TBG) concentrations while oral androgens decrease TBG. Transdermal preparations do not cause these effects because of absence of first passage of drug to the liver.
- b. *Salicylate, furosemide, and heparin*: salicylates > 20 g/d inhibit the binding of TH to TBG and transthyretin, decreasing the total T4 without affecting free T4. Clofibrate, heroin/methadone, and mitotane may cause decrease in serum TBG concentration. Large IV doses of furosemide (> 80 mg) may induce a transient increase in serum FT4 and a decrease in serum total T4 concentrations by inhibiting the T4 binding to its carrier protein. Heparin in standard subcutaneous doses (5000 U) may inhibit protein binding of T4.<sup>123</sup>

## 3. *Drugs interfering with L-T4 metabolism*

*Antiepileptic drugs*: phenytoin, carbamazepine, and phenobarbital may cause decrease in serum total T4 and FT4 concentrations due to increase in the metabolic clearance and hepatic metabolism of T4. *Psychotropic drugs*: sertraline lowers serum T4 concentrations and raises serum TSH.<sup>123</sup>

immunoglobulins. These maternal autoantibodies persist even after mothers with GD undergo definitive treatment with radioablation or thyroidectomy.<sup>127</sup>

## Diagnosis

The diagnosis of fetal thyrotoxicosis is suspected if there is fetal tachycardia and intrauterine growth retardation in a mother with active GD or in a mother with a history of GD or autoimmune thyroid disease, especially if she had clinically apparent ophthalmopathy. Maternal anti-thyrotropin receptor antibodies should be measured in at-risk pregnancies. Fetal heart rate and growth should be monitored by regular prenatal ultrasounds. Highly experienced ultrasonographers can often visualize the fetal thyroid that may be enlarged.<sup>128</sup>

Neonates with thyrotoxicosis are tachycardic, flushed, diaphoretic, and hyperkinetic. Goiter is common which if severe, can endanger the infant's airway. Diarrhea, vomiting, poor weight gain, and a transient exophthalmos may be seen. Arrhythmias and/or congestive heart failure can develop. The diagnosis of congenital hyperthyroidism is confirmed with profile of elevated free T4 and T3 and suppressed TSH in comparison to the standard value for gestational age.

The use of maternal antithyroid medications near the time of delivery or the co-transfer of maternal antithyroid blocking immunoglobulins may delay the appearance of neonatal Graves'. For high risk-infants, such as infants born to mothers with high levels of TSH receptor-antibodies or infants with a history of an affected sibling, it is recommended to obtain thyroid function tests at birth and at 1 and 2 months of age. For infants exposed to maternal antithyroid drugs in the third trimester, an additional set of thyroid hormones should be drawn at 1 week of age.<sup>128</sup>

## Differential Diagnosis

The differential diagnosis of neonatal thyrotoxicosis includes the McCune–Albright syndrome and activation mutations of the TSH receptor. These non-autoimmune etiologies are exceedingly rare but should be considered if thyrotoxicosis persists beyond 3 months of age.<sup>111</sup>

## Management

In diagnosed cases of fetal hyperthyroidism, antithyroid drugs are administered to the mother since these agents cross the placenta and inhibit the fetal thyroid function. There are two main types of antithyroid medication: propylthiouracil (PTU) and methimazole.

## Hyperthyroidism

### Neonatal Graves' Disease

### Epidemiology/Pathophysiologies

Fetal and neonatal Graves' disease (GD) is the most common cause of fetal/neonatal hyperthyroidism. It has been estimated that about 0.2% of pregnant women have GD; however, only 1% of children born to women with Grave's disease are found to have hyperthyroidism. Overt neonatal hyperthyroidism is rare and concerns only one neonate out of 50,000.<sup>127</sup> It affects both sexes equally. Fetal and neonatal GD result from the transplacental passage of thyroid-stimulating

These agents inhibit thyroid hormone synthesis by interfering with the function of thyroid peroxidase. PTU has an additional action of inhibition of deiodination of T<sub>4</sub> to the more active thyroid hormone T<sub>3</sub>. During pregnancy, PTU is the preferred therapy during the first trimester because methimazole has been shown to cause fetal malformation. Maternal ingestion of methimazole is associated aplasia cutis congenita, esophageal atresia, and umbilical abnormalities in the fetus.<sup>128</sup>

Treatment of neonatal hyperthyroidism is with PTU at 5–10 mg/kg/d or methimazole at 0.5–1 mg/kg/d, orally or per nasogastric tube in divided doses every 8 h. Inorganic iodine will speed up the fall in circulating hormone, therefore saturated solution of potassium iodide (SSKI) (48 mg iodide per drop) at the dose of one drop per day or Lugol's iodine solution (8 mg of iodine per drop) may be given in a dose of 1–3 drops daily.<sup>128</sup> Iodine solutions suppress thyroid hormone synthesis and thyroid hormone secretion. Iopanoic acid or sodium ipodate have also been used for their iodine content and their capacity to inhibit the activation of T<sub>4</sub> to T<sub>3</sub>. As in older patients, adjunctive therapy with beta-blockade and glucocorticoids may be used for symptom control until thyroid hormone levels are normalized. Propranolol may be given at a dose of 2 mg/kg/d. It inhibits actions of thyroid hormone resulting from T<sub>4</sub>-induced increased production of B-adrenergic receptors as well as inhibition of deiodination of T<sub>4</sub> to T<sub>3</sub>. In severe cases, prednisone can be given at a dose of 2 mg/kg/d.<sup>129</sup> It suppresses deiodination of T<sub>4</sub> to T<sub>3</sub> and compensates for T<sub>4</sub>- and T<sub>3</sub>-induced hypercatabolism of the endogenous glucocorticoids. If cardiac failure is present as part of neonatal hyperthyroidism, digoxin treatment is useful.<sup>128</sup>

## Prognosis

Neonatal GD has potential long-term morbidity which includes growth retardation, craniosynostosis, impaired intellectual function, and central hypothyroidism. The half-life of maternal immunoglobulin is approximately 14 days, so most cases of neonatal Graves will resolve after 3–12 weeks (depending upon the initial level of TSH-receptor antibodies).

Neonatal thyrotoxicosis resulting from activating mutations of the TSH receptor or of the alpha-subunit of the stimulatory G-protein persist beyond weeks and months whereas typical neonatal Graves' disease may have already remitted. Thyrotoxicosis due

to these mechanisms requires ablative treatment such as thyroidectomy.<sup>111,128</sup>

## Acquired Hyperthyroidism

### Epidemiology

Hyperthyroidism is uncommon but a serious condition in children and adolescent. It has a yearly incidence of 8 per 1,000,000 in children less than 15-year old and 1 per 1,000,000 in children less than 4-year old. It peaks between 10 and 14 years. Graves' disease (GD) is the most common etiology. Girls are affected four to five times more frequently than boys, although no gender difference is noted under 4 years of age.<sup>129</sup>

### Pathophysiology

Hyperthyroidism is caused by thyroid-stimulating antibodies that bind and activate the TSH receptor, leading to follicular cell hyperplasia and the hypersecretion of thyroid hormone. Autoantibodies directed against thyroglobulin, thyroid peroxidase, and the sodium-iodine symporter may also be present. Lymphocytic infiltration of the thyroid is present, hence its classification as a form of thyroiditis. Occasionally, germinal centers form, which can develop as a major source of intrathyroid antibodies. Lymphocytic infiltration and the accumulation of glycosaminoglycans in the orbital connective tissue and skin cause the extrathyroidal manifestation of Graves' ophthalmopathy and dermopathy, respectively.<sup>130,131</sup>

### Clinical Presentation

The presentation of Graves' disease in childhood may be insidious and a careful history will often reveal a several month history of progressive symptoms. Common complaints include nervousness, hyperactivity, heat intolerance, sleep disturbances, and a decline in school performance. A goiter is palpable in majority of cases, characterized by diffuse enlargement which is smooth, firm, and nontender. A bruit may be audible secondary to increased blood flow through the gland. Extrathyroidal manifestations such as ophthalmopathy and dermopathy are rarer than in adults and tend to be less severe. The pediatric literature cites a 25–60% frequency of ocular manifestations, but the majority is mild signs such as lid retraction, "staring," and slight proptosis that can be

attributed to the pseudosympathetic hyperactivity of thyrotoxicosis rather than true infiltrative disease of the orbital structures.<sup>129</sup> As expected, these signs improve in most patients after restoration of the euthyroid state. Unique to pediatric Graves' disease is the acceleration of linear growth and bone maturation associated with prolonged hyperthyroidism.<sup>129</sup>

## Diagnosis

Graves' disease presents with thyrotoxicosis or excessive quantities of circulating thyroid hormone. The constellation of thyrotoxicosis, goiter, and orbitopathy is pathognomonic of this condition. No additional laboratory tests or imaging studies are necessary to confirm the diagnosis. If thyromegaly is subtle and eye changes are absent, an I<sup>123</sup> uptake, with or without scan, can be performed.<sup>111</sup>

## Differential Diagnosis

The differential diagnosis of thyrotoxicosis or hyperthyroidism includes transient thyroiditis, hyperfunctioning nodule(s), and thyrotoxicosis factitia. In the majority of cases, the presence of a symmetrically enlarged thyroid coupled with the chronicity of symptoms will be adequate to allow a diagnosis of Graves' disease but radionuclide studies showing increased generalized uptake on I<sup>123</sup> scan can provide confirmatory data.<sup>111</sup>

## Management

Children with GD can be treated with antithyroid medication such as methimazole, radioiodine therapy using <sup>131</sup>I, or thyroidectomy. Lasting remission after antithyroid therapy occurs in only a small minority of pediatric patients with GD. However, since some children will go into remission, methimazole therapy is still considered the first line of therapy for most children.<sup>132</sup> Properly administered radioactive iodine is an effective treatment of GD in children. However due to risk of thyroid cancer after external radiation being highest in children <5 years of age, <sup>131</sup>I therapy should be avoided in this age group.<sup>132</sup> Thyroidectomy is an effective treatment for GD, but it is associated with a higher complication rate in children. It should be performed by a high-volume thyroid surgeon with experience in doing thyroidectomies in children.<sup>132</sup>

## Anti-thyroid Medications

The thionamide derivatives, methimazole and propylthiouracil/PTU are the most commonly used antithyroid drugs in the US. Both inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin, thus block thyroid hormone biosynthesis. PTU has the additional action of inhibiting the extrathyroidal conversion of T4 to T3.<sup>133</sup> Due to higher risk of hepatotoxicity related to PTU, methimazole is the preferred antithyroid therapeutic agent for Graves' disease in children and adolescents. If used as first-line of therapy, antithyroid medication should be administered for 1–2 years; remission has only been reported in 30% of patients.<sup>133</sup> The recommended starting dose is 0.5–1.0 mg/kg/d for methimazole and 5–10 mg/kg/d per day for PTU divided into three doses. Side effects reported due to anti-thyroid medications aside from hepatic failure include agranulocytosis, polyarthritis, vasculitis, and minor side effects such as skin reactions, arthralgias, and gastrointestinal discomfort.<sup>133</sup>

## Definitive Therapy

For patients, who do not go into remission on methimazole therapy, or who are not able to tolerate or are unlikely to respond to antithyroid medications, the two options for definitive treatment of Graves' disease are <sup>131</sup>I therapy and thyroidectomy. Both are likely to result in life-long hypothyroidism.

### <sup>131</sup>I Therapy

Due to increased risk of thyroid nodules and cancer with low level thyroid irradiation in children and poor remission rates with low-administered levels of <sup>131</sup>I, it is recommended that larger (> 150 µCi of <sup>131</sup>I per gram of thyroid tissue) rather than smaller activities of <sup>131</sup>I to be administered to achieve hypothyroidism.<sup>132</sup> After <sup>131</sup>I therapy, T3 and T4 and or estimated free T4 levels should be obtained every month. Because TSH may remain suppressed for several months after correction of hyperthyroid state, TSH determination may not be immediately useful in assessing hypothyroidism. Hypothyroidism typically develops by 2–3 months post treatment, at which time L-thyroxine should be prescribed. Side effects of <sup>131</sup>I therapy (<10% complain of mild tenderness over the thyroid for the first week after therapy) are uncommon except for lifelong hypothyroidism that is the goal for therapy. There is no evidence to suggest that children and adults treated for GD with more than 150 µCi of <sup>131</sup>I per gram



of thyroid tissue have an increased risk of thyroid cancer.<sup>132</sup>

## Thyroidectomy

Surgery is an acceptable form of therapy for GD in children. It is the preferred treatment for GD in young children (<5 years) when definitive therapy is required and in individuals with large thyroid glands (>80 g) when the response to <sup>131</sup>I may be poor.<sup>132</sup> The surgery should be performed by a high volume thyroid surgeon. Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of methimazole; it should be given 1–2 months in preparation for thyroidectomy. Potassium iodide should be given in the immediate preoperative period. The recommended procedure must be a total or near-total thyroidectomy.<sup>132</sup>

## Thyroid Nodules and Thyroid Cancer

### Thyroid Nodules

#### Epidemiology

Thyroid nodules are rare in children with an incidence rate of 0.46–1.5%. Solitary nodules in children have a 20–25% prevalence of malignancy.<sup>134</sup> This malignancy risk in children is fourfold greater than the risk among adults. Risk factors for the development of thyroid nodules include female sex, pubertal age, family history of thyroid disease, previous or coexisting thyroid disease, and previous radiation exposure.

#### Benign Thyroid Nodules

Follicular adenomas, colloid cyst, lymphocytic thyroiditis, and thyroglossal duct cysts are among the benign thyroid nodules.<sup>134</sup> Some benign thyroid nodules can cause overactivation of the gland or compression signs of the nearby organs in addition to causing cosmetic problems. Some nodules associated with Hashimoto thyroiditis are also associated with hypothyroidism.

All adenomas can be classified under follicular adenomas. Approximately 1% of thyroid adenomas are toxic adenomas. Toxic adenomas, also known as hyperfunctioning adenoma are follicular adenomas with a clinical evidence of hyperfunction.

### Diagnosis and Management of Thyroid Nodules

Evaluation of a solitary nodule almost always warrants a fine-needle aspiration under ultrasound

guidance. Excisional biopsy may be considered over FNA if there is history of exposure to radiation, family history of thyroid cancer or if there are exam findings consistent with malignancy such as rapid growth or a firm fixed nodule.<sup>134</sup> Thyroid nodules which are found on aspiration cytology to be benign can be followed by repeated physical examination and neck ultrasounds. Any enlargement in the size of the nodule would warrant a repeat fine-needle aspiration or surgical removal. For many years thyroxine therapy trying to suppress the size of the nodule has been used. However, a decrease in size is observed in well-differentiated cancerous lesions and is likely due to TSH responsiveness in malignant cells.<sup>134</sup> Fine-needle aspiration, which is safe and simple procedure, is better than suppressive therapy in differentiating benign versus malignant nodules. The accuracy of the FNA depends on careful aspiration, smear preparation and microscopic evaluation, and on the experience of the cytologist.

In untreated individuals with thyroid nodules, approximately 50% of thyroid nodules decrease in size or disappear, 30% remain the same, and 20% increase in size. Those that decrease in size are mostly cystic lesions and those that grow are particularly likely to be malignant.<sup>1</sup>

## Thyroid Cancer

### Epidemiology

Pediatric thyroid cancer is a rare and treatable disease with an excellent prognosis. The incidence of thyroid cancer in children and adolescents has been estimated to be between 0.2 and 3 cases per million per year. The thyroid cancer types in children in the US are 60% papillary thyroid cancer, 23% follicular variant of papillary, 10% follicular thyroid cancer, and 5% medullary thyroid cancer. Papillary and follicular thyroid cancers constitute differentiated thyroid cancer. These present at more advanced stages of disease in children compared to adults and are associated with higher rates of recurrence.<sup>1</sup>

### Pathophysiology

**Environment.** Radiation exposure is a well-established environmental risk factor that promotes thyroid cancer. Approximately 36% of all pediatric patients who have been diagnosed with thyroid cancer were diagnosed during the first half of the 20th century, when radiation

treatment was used to treat benign conditions such as thymic enlargement of infancy, tonsillar and adenoid infections, and tinea capitis. The incidence of thyroid cancer decreased after discontinuation of routine radiation for these benign conditions. However, the incidence of thyroid nodule was unchanged. Hodgkin's disease survivors had thyroid nodules 27 times more frequently than did their siblings.<sup>135</sup> Among 1791 patients studied, the relative risk of developing thyroid cancer was 18.3-fold greater than the risk in the general population. There are also reports of thyroid adenoma/carcinoma developing after treatment for childhood leukemia and other malignancies. Therefore, these children should be followed closely for the development of thyroid cancer.<sup>135,136</sup>

Thyroid carcinoma may occur in the context of autoimmune disease. Up to 38% of patients with thyroid cancer can have coexistent Hashimoto's thyroiditis.<sup>137</sup> Cancer rate is estimated to be between 1% and 9% in patients with Graves' disease.<sup>138</sup> Thus, prominent nodularity in the thyroid gland of a patient with autoimmune thyroiditis warrants evaluation.<sup>137,138</sup>

## Genetics

Nonmedullary or differentiated thyroid carcinoma such as papillary and follicular carcinomas are less frequently inherited than medullary thyroid carcinoma. Only approximately 5% of nonmedullary cancers are inherited. There is a high risk of thyroid papillary carcinoma, especially the sisters of probands with papillary carcinomas.<sup>140</sup> Thyroid adenocarcinoma was noted to be associated with melanoma and with other connective tissue tumors. Associations were also found between thyroid carcinoma and cancers of the colon, breast, ovary, and kidney.<sup>139,140</sup>

Inherited nonmedullary thyroid cancers may occur in a number of heritable syndromes such as familial adenomatous polyposis,<sup>141</sup> Cowden disease,<sup>142</sup> Carney complex,<sup>143</sup> and Bannayan-Ruvalcaba-Riley syndrome.<sup>144</sup>

Medullary thyroid carcinoma (MTC) is more likely to be inherited than the differentiated thyroid carcinomas. MTC arises from the parafollicular cells or C cells of the thyroid gland that produce calcitonin. MTC is caused by autosomal-dominant gain of function mutations in the RET protooncogene on Chromosome 10. Numerous mutations of the RET protooncogene have been identified and found to correlate with disease type and tumor aggressiveness.

Hereditary forms of MTC account for about 30% of cases of MTC and include the following genetic syndromes: multiple endocrine neoplasia Type 2 (MEN2A), MEN2B, and familial medullary thyroid carcinoma (FMTC). MEN2A includes multicentric and usually bilateral MTC, unilateral or bilateral pheochromocytoma, and hyperparathyroidism, due to parathyroid hyperplasia or adenoma.<sup>30</sup> MEN2B includes medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas of the alimentary tract and subconjunctival areas, and skeletal abnormalities including marfanoid habitus, pectus excavatum, and slipped capital femoral epiphysis.<sup>30</sup> MTC in MEN2B presents at a younger age than does that in MEN2A and in FMTC; not infrequently it is detectable in infancy.<sup>145</sup> MEN2 B-associated MTC is also more aggressive than the medullary thyroid cancer associated with MEN2A or with FMTC.<sup>145</sup>

## Diagnosis and Management

The most common presenting feature of thyroid carcinoma in children and adolescents is an asymptomatic thyroid mass. Another is a solitary asymptomatic lateral cervical mass.<sup>146</sup> When thyroid nodules are detected, serum TSH, free T4, and a thyroid ultrasound should be obtained. If the TSH is suppressed, a radionuclide scan may identify a hyperfunctioning nodule. Thyroid ultrasound characteristics suggestive of malignancy include microcalcifications, indistinct margins, and a variable echotexture. Ultrasound can determine the intrathyroidal location of nodules, identify additional nodules, and assess whether there is lymph node involvement. However, ultrasound appearance alone cannot reliably distinguish between benign and malignant lesions. Thus, fine-needle aspiration (FNA) is indicated for children with thyroid nodules. Ultrasound-guided FNA is the most accurate means to evaluate if a thyroid nodule is malignant. Total thyroidectomy along with selective neck dissection for regional metastatic disease is recommended for thyroid carcinoma.<sup>146</sup> This is followed by nuclear scintigraphy with subsequent radioablation for residual or recurrent disease and thyroid suppression and/or thyroid hormone replacement.

It is standard practice to treat thyroid cancer patients with L-thyroxine postoperatively, since it is well-recognized that TSH suppression can reduce

recurrence of the cancer. Follow-up care of child with differentiated thyroid carcinomas involve periodic monitoring of thyroid hormone levels, neck ultrasound, measurement of thyroglobulin (indicator of residual thyroid gland), and whole body radioiodine scan.

Regarding MTC, serum calcitonin is the most reliable marker. Genetic testing for RET protooncogene is needed in families with history of MTC and treatment is based on mutation present. Mutation analysis is used to determine the timing of surgery so that surgery can be performed before the onset of malignancy. Patients with MEN should be screened and undergo long-term monitoring for hyperparathyroidism (MEN 2A only) as well as for pheochromocytoma (both MEN 2A and 2B).<sup>30</sup>

Many childhood endocrine disorders require an index of suspicion to identify the disorder(s) in a timely manner because symptoms can be quite variable. The primary care clinician sees children with undifferentiated problems, not diagnoses, so careful observation of growth and, development and clinical presentation is critically important. Pediatric endocrinology is evolving with new treatment options that improve outcomes for children with endocrine disorders and this overview aims to assist busy primary care clinicians in their efforts to provide exemplary care in the diagnosis and management of children with endocrine disorders.

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